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CLASSIFICATION OF MAMMARY CARCINOMAS TO INDICATE PREFERABLE THERAPEUTIC PROCEDURES[1]

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IT is often difficult, if not impossible, to evaluate the different therapeutic procedures which have been employed in the treatment of mammary carcinomas because but few statistical reports are based upon series of cases classified either from clinical or pathologic aspects. This point has been illustrated on several occasions by a table which I compiled from the reports of many surgeons about the results which they have obtained by operations during the past 20 years (Table I). The five-year survival rates vary from 15 to over 50 per cent, and the mean average is about 28 per cent. Such a wide variation in the results obtained by indisputably competent surgeons from well accredited hospitals and clinics may indicate that different surgeons may have selected for operation patients with different types of carcinomas and that those who report comparatively low survival rates operated upon patients with more advanced disease than did these reporting the higher rates. This explanation of the variations is probably correct because each surgeon had the same anatomical limitations, and the types of surgical procedures used probably would not generally vary a great deal.

TABLE I.—SURGICAL CURABILITY OF CANCER OF THE BREAST: FIVE-YEAR SURVIVALS

Author	Per cent	Author	Per cent
Lee and Cornell	15.0	Faure	28.2
Rahm	15.9	Hoffmann	28.5
Lindner	17.0	Halsted	28.9
Smith	17.0	Buchanan	29.0
Gibson	18.0	Black	30.0
Hartmann and Bergeret	19.0	Deelman	30.6
Grassmayer	20.3	Braine and Massie	31.0
Tichy	20.9	Morton	31.0
Schwarzkopf	21.0	Lindenberg	31.4
Neber	21.0	Steinthal	33.3
Forgue	22.0	Moschocowitz *et al*	34.0
Brattström	23.0	Schoute and Orbaan	35.9
Broeström	23.0	White	36.0
Bunts	24.1	Iselin	36.4
Sadlier	24.3	Smith and Bartlett	37.0
Dahl	24.5	Crile	37.4
Jennings	25.0	Peck and White	39.1
Harrington	25.8	Judd	39.8
Greenough	27.0	Mills	39.8
Perthes	27.7	Primrose	44.4
Gernade	28.0	Wintz	48.5
Lehmann	28.0	Watson-Cheyne	52.1

Mean average = 28.0 per cent

It is just as difficult to draw conclusions about the effectiveness of irradiation in the treatment of mammary carcinoma when the cases are not classified. In addition, many reports which compare the results secured in irradiated and non-irradiated cases are made by individuals who are not well informed about radiological procedures, and usually they have not taken into consideration when, why, or how irradiation was administered.

When the results of treatment are reported, especially from a prognostic standpoint, the importance of classifying malignant diseases on some generally acceptable basis is illustrated by the advantages which have come from grouping cases of carcinoma of the uterine cervix. When good results in the treatment of carcinomas of the cervix were first reported by radiolo-

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gists there was considerable skepticism among surgeons and even animosity toward radiological procedures. This led to the classification of cases in order that operative results might be compared on an equitable basis with results obtained by radiological methods. A number of years ago the American College of Surgeons adopted a classification which has proved quite satisfactory and has been generally accepted in this country, because those who used it knew what each different group represented, and there was mutual understanding. Furthermore, it was applicable for prognostication and for the equitable comparison of different methods of treatment. It will be recalled that this classification for carcinoma of the cervix is based upon the stage of the disease or its extent at the time of treatment.

Peculiarly enough, no such plan has yet been accepted for the classification of cases of mammary carcinoma. I believe that it would be advantageous to adopt some plan for grouping cases of mammary carcinoma so that, in the future, better information will be available upon which to base prognosis and to indicate what therapeutic procedures have been found to be preferable as well as to establish greater uniformity in publications about comparative results. Such a classification might be based upon a correlation of the interrelated clinical and pathologic aspects of the disease.

I would like to discuss some of the methods which already have been suggested for classifying mammary carcinomas.

Pathologists have attempted to classify carcinomas of the breast according to histogenesis and morphology. As far as histogenesis is concerned, it must be conceded that all carcinomas originating in the mammary gland itself must develop in or from the epithelial cellular elements of the lacteal duct system. There may be other carcinomas which affect the mammary gland secondarily but which do not originate in gland structures. However, some carcinomas which originate in one part of the mammary duct system vary in morphology from others of similar origin, and many carcinomas which apparently are of a certain anatomical derivation may present quite different histologic characteristics in different areas of the tumor. Therefore, since classifications of mammary carcinomas on the basis of histogenesis alone are fallible, pathologists are forced to distinguish them by applying descriptive adjectives to characterize differences in the histologic appearances. This often results in confusion when the clinician tries to interpret physical manifestations or the clinical course in accordance with these various adjectives which describe morphology but give no intimation of the extent of the disease.

The eminent authority in pathology, Dr. James Ewing (1), has recently suggested the following classification for mammary carcinomas:

1. Adenocarcinoma arising in cysts;
2. Mucous or gelatinous carcinoma;
3. Duct carcinoma:
   (*a*) Localized duct carcinoma: comedo-carcinoma,
   (*b*) Diffuse duct carcinoma;
4. Paget's disease;
5. Carcinoma arising on chronic mastitis;
6. Sweat-gland cancer;
7. Inflammatory carcinoma;
8. Histologic designations:
   (*a*) Medullary carcinoma,
   (*b*) Scirrhous carcinoma,
   (*c*) Fibrocarcinoma,
   (*d*) Carcinoma *en cuirasse*,
   (*e*) Carcinoma simplex.

In this plan an attempt is made to establish a classification of mammary carcinomas according to histogenesis, but this proves to be too difficult, and therefore, terms employed to specify histogenesis are intermingled with clinical terminology and adjectives describing morphology. For example, the words "mucous" and "gelatinous" are descriptive adjectives, yet "mucous or gelatinous carcinoma" is given individual identity in this classification, although either adenocarcinoma, arising in cysts, or duct carcinoma, otherwise quite different morphologically and histogenically, may produce intracellular mucus or gelatin.

Paget's disease is classed as a carcinoma, yet this condition of the nipple which Paget first described apparently may be benign at one time and malignant at another; hence, a clinical term is applied as if it were a pathologic entity. The same applies to carcinoma *en cuirasse*. This is a clinical description meaning that a malignant process has extended around the trunk, which is probably not a characteristic of only one morphologic type. "Sweat-gland cancer" may or may not be primarily a mammary gland carcinoma yet it may affect the breast and there often is uncertainty as to its histogenesis. There also may be some dispute about "inflammatory carcinoma" as an entity because different morphological types of mammary carcinomas apparently may present clinical manifestations which conform to the classical clinical definition of inflammation, namely, pain, heat, redness, and swelling.

Such a classification may be eminently satisfactory for pathologists, but I believe that classifications which are based on our present knowledge of histogenesis, histologic characteristics, or the cytology of neoplasms cannot be applied clinically with satisfaction and consistency to establish prognosis or indicate therapeutic procedures for different types of growth. The principal objections are that tumors of apparently the same origin may present one or several different types of morphology, and there is no way to determine with accuracy the anatomical extent of the disease by the histologic characteristics of a neoplasm.

In addition to the commendable efforts of pathologists to classify mammary carcinomas according to histogenesis or morphology, some have been interested in grouping or grading them according to variation in some of their histologic characteristics which may indicate differences in degrees of differentiation or anaplasia and, therefore, differences in degree of malignancy. This idea was suggested as early as 1893 by David P. von Hausemann (2) who taught that the degree of anaplasia of neoplastic cells was an index of the degree of malignancy and was of prognostic significance. Other suggestions about histologic characteristics which might indicate the degree of anaplasia have been described and advocated as a basis for classifications or grading of neoplasms. C. D. Haagensen (3) recently collected 15 such suggestions from the medical literature and applied each to a remarkably well organized and controlled series of cases of mammary carcinomas. He found that only six histologic characteristics had prognostic significance, and he tabulated them in the following manner:

1. Papillary character: origin in a cyst formed in a duct;
2. Comedo character: growth mainly in ducts, often with central necrosis;
3. Adenoid arrangement of cells:
   (*a*) Marked,
   (*b*) Slight,
   (*c*) Absent;
4. Variations in size and shape of nuclei:
   (*a*) Slight,
   (*b*) Moderate,
   (*c*) Marked;
5. Number of mitoses:
   (*a*) Few,
   (*b*) Moderate,
   (*c*) Numerous;
6. Gelatinous degeneration.

If we attempt to classify mammary carcinomas on the basis of differences in morphology or histologic characteristics, it must be done after removal of the tissues and not on the basis of any clinical information, and again we encounter descriptive adjectives and also uncertainty among different individuals as to the degrees of anaplasia in any one neoplasm and even divergent opinions about different areas in a single tumor. As a result of his studies, Haagensen concluded that histologic grading "is only an approximation, and a rough one at that" and "should not be regarded as in any sense competing with clinical data bearing on prognosis to which it is, of course, subordinate in importance." In discussing this presentation, Dr. Ewing evidently concurred in this opinion. He said: "When it comes to predicting what will happen to a patient, certainly no pathologist and no clinician will ever say that histological grad-

ing will give us the information that can be obtained from the clinical index."

It must be apparent that one of the chief difficulties which will be encountered in classifying carcinomas according to their degrees of differentiation from a prognostic standpoint, will be due to the fact that some patients with histologically highly malignant anaplastic but localized neoplasms which are completely removed, survive while others with much less malignant and differentiated growths succumb to the disease. This can be explained only on the basis of differences in the extent of the disease in each instance. Therefore, unfortunately, we cannot depend upon these microscopic evidences as a basis for satisfactorily classifying cases of mammary carcinoma in order to indicate the prognostic or the preferable therapeutic procedures, although when the degree of anaplasia in a neoplasm can be ascertained, the rate at which dissemination may take place may be indicated.

These considerations lead us to contemplate the possibility of classifying cases of mammary carcinoma solely on the basis of information obtained about the extent of the disease by clinical examinations.

Several methods for classifying cases of mammary carcinoma on purely clinical findings have been published. Perhaps one of the first which was favorably received was that of C. F. Steinthal (4) who grouped a series of cases in the following manner:

Group I: Those having a tumor, apparently growing very slowly, and measuring only a few centimeters in diameter, entirely confined to the mammary gland; the skin is not yet attached and the axillary nodes are few in number and are first discerned only at operation.

Group II: Those with definitely growing tumors which, after remaining stationary for some time, begin to increase in size; the skin becomes adherent, and nodes in the axilla are definitely demonstrable.

Group III: Those in which a large part of the mammary gland has become involved, the tumor has invaded the skin and underlying structures, and frequently the supraclavicular nodes are also involved.

A few criticisms of the method may be offered. In Group I are tumors "apparently growing very slowly." Unfortunately, the rate of growth, especially of small tumors in the breast, often is very difficult to determine with satisfactory accuracy because conclusions must be based upon the notoriously inaccurate observations and ignorance of most women about their anatomy. In many cases clinicians have reason to believe that a breast tumor has existed much longer than can be determined from the personal history. Secondly, the size of a tumor is no indication of the extent of the disease because not infrequently distant metastases will be found from tumors that are "only a few centimeters in diameter," and large tumors may not metastasize until relatively late. Thirdly, some cases are included in this group in which "the axillary nodes are few in number and are first discerned only at operation." The presence of axillary metastases contradicts the previous postulate that the disease should be "entirely confined to the mammary gland." Experience indicates, and I hope to demonstrate, that when a mammary carcinoma has extended to the axillary nodes in any degree, the condition is less favorable than if the growth is still localized entirely within the breast.

In addition, in Steinthal's Group II we find again that difficulty of deciding about the rate of growth of a tumor and of ascertaining if "nodes in the axilla are definitely demonstrable." On the basis of our studies and the reports of others, I believe that axillary metastases will be found in from 70 to 75 per cent of all cases. In our series, their presence was definitely demonstrable clinically in only about half of those patients who had them. Also, there may be uncertainty about axillary involvement in many cases even after gross examination of tissues removed at operation and not infrequently microscopic examination gives the only reliable confirmation. Therefore, I believe that when there are no axillary metastases, cases should be placed in an

entirely different category from those in which there is any degree of axillary involvement, and that this can be ascertained only after careful search and microscopic examination.

Another interesting and ingenious method of classifying mammary carcinomas, especially for prognostic purposes, was suggested by B. J. Lee and J. G. Stubenbord (5).

	Weighting Factor	Gradation Factor	
Age	A = 2	Over 55	= 1
		A_G 41–55	= 2
		40 or under	= 5
Lactation	L = 3	Absent	= 0
		L_G Present	= 3
		Slow	= 1
Rate of Growth	R = 4	R_G Moderate	= 2
		Rapid	= 4
		Small, 3 cm.	= 1
Extent of Disease	E = 5	E_G or less	
		Large	= 2
		Nodes present	= 4

$$C.I.M. = 2A_G + 3L_G + 4R_G + 5E_G$$

Grade A—C.M.I. = 11 to 25—relatively benign.

Grade B—C.M.I. = 26 to 39—moderately malignant.

Grade C—C.M.I. = 40 to 55—highly malignant.

This scheme is established on certain clinical findings to which numerical evaluations are assigned, according to what experience has proved may be their relative significance in prognosis. A summation of these values, in any case, places it in one of three grades or groups, each of which has a different total valuation.

According to this plan of classification, it is apparently assumed that a definite diagnosis of mammary carcinoma is already established, but to distinguish between benign and malignant tumors in the breast is not always easy.

We also find in this plan several variables and some factors which depend upon the personal history rather than definite physical evidences of the disease, and therefore the method is subject to criticism.

The first weighting factor employed is based upon the age of the patient, and the corresponding gradation values are apparently established upon the theory that the younger the patient the more malignant a carcinoma will prove to be, because the ages under 40 are given a relatively very high value compared with the values given to ages of 55 or over. It must be conceded that mammary carcinomas usually appear to grow more rapidly in younger rather than in older women. However, given two patients, one under 40 and one over 55, each with a localized carcinoma of the same size and without metastases, the prognosis for each will be exactly the same if each tumor can be removed completely; that is, both patients probably will survive. In other words, it is the extent of the disease at the time of treatment that is of prime importance rather than the age of the individual, other factors being the same.

Experience seems to indicate that the second weighting factor, lactation, has some bearing upon the rate of dissemination of mammary carcinomas, yet if malignant neoplasms can be removed completely from a lactating breast before they have extended outside the gland, the prognosis is just as good as in a quiescent organ. But, unfortunately, the neoplastic processes that develop in the breast at the time of pregnancy are usually considered to be associated with certain phases of the physiologic activity of the gland and the neoplastic process may be overlooked by both patient and physician until the growth has had time to be widely disseminated and the patient is in a hopelessly incurable condition. Lactation may be of significance when present but is of very little significance when absent. According to our experience, carcinoma has occurred in lactating breasts in much less than 2 per cent of all cases.

The third weighting factor of rate of growth depends to a great extent upon the history, or time at which the patient thinks she discovered the tumor, and her own estimation of the rate at which it enlarged. This is seldom conclusive or even satisfactory evidence.

The fourth weighting factor concerns

the extent of the disease, and this is established, first, upon a tumor size of three centimeters less or more, and second, upon the presence of axillary nodes. I believe that it seldom is possible to estimate the dimensions of a tumor in the breast with accuracy by clinical examination in comparison to its actual size and certainly not within two centimeters. Also, very large carcinomas may occur in the breast, especially of the type which originate in papillary cysts, without any evidence whatsoever that the disease has extended outside the mammary gland, and complete removal will apparently cure the patient. On the other hand, carcinomas less than three centimeters in diameter may have metastasized before they are discovered. The question of the presence or absence of involvement of the axillary nodes has previously been discussed, but I may repeat that the presence of axillary metastases can be predetermined in only about one-half the patients who have them.

I am fully aware that any method for classifying mammary carcinomas is subject to criticism, yet I am bold enough to suggest still another which is based upon both clinical and pathological evidences of the extent of the disease. We have found this method to be practical for the interpretation of the extent of the disease as determined by physical examination, it indicates the prognosis with satisfactory consistency, and it is especially useful in obtaining uniformity in a statistical review of cases. I would like to discuss this classification also as a means of indicating what therapeutic procedures I think are preferable for different groups of patients according to our modern concepts of the treatment of malignant diseases, by making deductions from our own series of cases.

This classification was developed when Dr. Allen Graham, pathologist at the Cleveland Clinic, made a very thorough study of all cases of mammary carcinoma operated upon by the members of our surgical staff. He arrived at a very definite conclusion, namely, that these cases could be divided into four groups according to certain manifestations of the extent of the disease and the prognosis in individual cases could be based on these findings (6). I employed a similar classification in studying and comparing the results obtained in a series of these cases in which operation was the only treatment and in another series in which post-operative roentgen radiation was given (7). However, I divided the cases into only three groups, the difference being that Dr. Graham made a separate group of those with histologic evidence of malignancy but without gross tumor in the breast and no axillary metastases, while I, for the sake of simplicity, included in one group such cases as well as those in which tumor was also present in the breast without axillary metastases. The classification is arranged as follows:

Group I

(*a*) *Tumor* definitely localized in the breast and movable;
(*b*) *Skin* not involved;
(*c*) *Metastases* not present in axillary lymph glands.

Group II

(*a*) *Tumor* localized in the breast and movable;
(*b*) *Skin* not affected (or only very slightly edematous or ulcerated);
(*c*) *Metastases* present in axillary lymph glands but few involved.

Group III

(*a*) *Tumor* diffusely involving the breast;
(*b*) *Skin* involved (edematous, ulcerated), multiple nodules;
(*c*) *Metastases* to numerous axillary lymph glands or to other tissue (supraclavicular nodes, lungs, bones, etc.).

This plan includes both clinical and pathological findings about the anatomical extent of the disease. We have found that it is necessary to take these two aspects into consideration because physical examination will reveal the presence of axillary metastases in only about one-half the cases in which they are present, and therefore a pathologist's examination is essential because the prognosis and indications for therapeutic procedures must depend upon this complete information about the extent of the disease.

It is obvious that usually it would be difficult—if not impossible—to distinguish our Group I from our Group II cases by physical evidences alone. But on the other hand, cases that would be classed in either of these two groups can usually be distinguished from Group III cases by clinical manifestations which are not so obscure. These will be discussed in greater detail later.

In order to illustrate the applicability of this classification to a large series of cases of mammary carcinoma, I would like to discuss our experiences to show (1) the relative proportion of cases in each group, and (2) the difference in the prognosis for each group on the basis of the therapeutic procedures employed.

I will use 405 cases of mammary carcinoma which were primarily operated upon by Dr. George Crile between 1895 and 1930, inclusive, and classified by Dr. Graham (Table II). The records were complete enough so that 92 per cent could be classified. Of these classifiable cases, 29.4 per cent were placed in Group I, 25.9 per cent in Group II, and 44.7 per cent in Group III.

Therefore, if we may use this experience as a basis for generalization, we may conclude that approximately 30 per cent of women with mammary carcinoma have no axillary metastases (Group I, 29.4 per cent), that one-quarter (Group II, 25.9 per cent) have axillary metastases with still localized movable tumors, that almost one-half have advanced carcinomas (Group III, 44.7 per cent), and that about 70 per cent of all patients have axillary metastases or even more extensive disease by the time they appear for operation (Group II plus III). No doubt the same relative proportions would be found in any large series of cases, as indicated by the reports in the literature that from 70 to 75 per cent of all patients with mammary carcinoma have been found to have axillary metastases.

Obviously, each of our groups has a different prognosis. This will be illustrated by two series of Dr. Crile's cases that I have studied in order to make a comparison between one series in which operation was the only treatment and another to which I gave roentgen therapy post-operatively. I will call the first series the non-irradiated group and the other the irradiated group. It is to be noted that his comparison will be based on two series of traced cases of mammary carcinoma in which only one surgeon operated upon each patient, and

TABLE II.—CARCINOMA OF THE FEMALE BREAST[1]: ALL CASES

Primary operations by Dr. George Crile, 1895–1931. (*Courtesy of Dr. Allen Graham.*)

	Total Cases		Operation Only Non-irradiated Series		Operation Plus Roentgen Therapy: Irradiated Series	
	No.	Per cent	No.	Per cent	No.	Per cent
Number of cases	405		170	42.0	235	58.0
Unclassifiable	32	8.0	27	16.0	5	2.0
Classified	373	92.0	143	84.0	230	99.8
Group I	110	29.4	52	36.3	58	25.2
Group II	96	25.9	26	18.2	70	30.4
Group III	167	44.7	65	45.5	102	44.4
Group II plus Group III (with axillary metastases)	263	70.6	91	63.7	172	74.8

[1] Exclusive of Paget's disease, sweat-gland cancer, papillary carcinoma, sarcoma.

TABLE III.—CLASSIFIED TRACED CASES FOR COMPARISON OF RESULTS

	Total Cases	Group I		Group II		Group III	
		No.	Per cent	No.	Per cent	No.	Per cent
Irradiated series: post-operative prophylactic roentgen therapy (1922–1931)	99	21	21.2	37	37.3	41	41.5
Non-irradiated series: operation only	85	21	24.7	23	26.0	41	48.3
Totals	184	42	22.8	60	32.6	82	44.6

one radiologist administered treatment more than five years ago according to one technic which was in vogue at that time. Both series have been classified on exactly the same basis according to the extent of the disease in each case. These two series should give a fair indication of what the prognosis would be for our different groups, as well as a just comparison of the results obtained in series of non-irradiated and irradiated cases. I would like to call attention to the fact that patients treated preoperatively or only for post-operative recurrence or metastases are not included in the irradiated series and only those given immediate post-operative roentgen therapy for what may be called prophylaxis are considered, whether they had only one or more complete courses of treatment (Table III).

Between 1922 and 1931, I gave post-operative roentgen therapy to 100 of Dr. Crile's patients. Unfortunately one patient did not return after her first course of treatment, and this case had to be discarded because we are discussing only traced cases; therefore, 99 cases remain in the irradiated series. I grouped these according to our classification and, interestingly enough, my conclusions conformed with those of Dr. Graham, who previously had classed them independently. This shows that our plan is satisfactory and consistently applicable by different individuals. It happened that the irradiated series arranged itself as follows: Group I contained 21 cases (21.2 per cent); Group II contained 37 cases (37.3 per cent), and Group III contained 41 cases (41.5 per cent). It will be noted that the relative proportions for each group in this irradiated series were not the same as the rates for the groups in the total series discussed previously. The disproportion lies in Group II which is larger in the irradiated series (37.3 per cent) than in the total series (25.9 per cent) because, after operation, when axillary metastases were found, more of such patients were referred for roentgen treatment than when metastases were absent.

After arranging the 99 non-irradiated cases into their proper groups, we tried to find among Dr. Crile's traced cases an equal number in each group, but none of these are reported to have received irradiation at any time. We found that so many of Dr. Crile's classifiable traced patients had had irradiation for one or another reason (85 per cent) that only 23 Group II cases were of use to make the comparison. However, there were more than enough for Group I (21) and exactly enough for Group III (41) cases. Therefore, in order to have the number of Group II cases equal in each series, I was forced to discard 14 cases from the irradiated series and chose to use the last 23 consecutive cases because more was known about these than the earlier cases.

In this way it became possible for me to study the prognosis and results of treatment in a total of 170 cases divided into non-irradiated and irradiated series, each series containing 85 consecutive cases, the cases in each series classified into three groups on the same basis according to the extent of the disease found to be present, and each different group in each series containing the same number of consecutive cases, every patient in each series operated upon by one surgeon and the cases in one of these series given post-operative roentgen therapy more than five years ago by one radiologist, using one technic. The two series were arranged for comparison as in Table IV.

According to this tabulation, 100 per cent of the patients in Group I survived for five or more years without evidence of the return of their disease following operation alone. It happened that one patient in the irradiated series died of cancer before that time. This case illustrates the possibility that axillary metastases may be absent and the disease disseminated through other lymphatic routes; for example, to the parasternal nodes, and therefore they are undetectable, or else axillary metastases escape the pathologist's examination. Either circumstance would occur but rarely.

It seems justifiable to conclude from this study that almost 90 to 100 per cent of the patients with mammary carcinomas but without metastases to the axillary lymph

TABLE IV.—KNOWN FIVE-YEAR RESULTS IN 85 NON-IRRADIATED CASES AND 85 SELECTED IRRADIATED CASES

(All Groups Equal. Results by Percentages)	Group I	Group II	Group III	All Cases
Number of cases				
Non-irrad.	21	23	41	85
Irrad.	21	23	41	85
Lost or died of cause other than cancer under 5 years				
Non-irrad.	23.7	8.7	12.2	14.1
Irrad.	14.3	8.7	9.7	10.6
Remaining for estimate of 5-year known results				
Non-irrad.	76.3	91.3	87.8	85.9
Irrad.	85.7	91.3	90.3	89.4
Known dead of cancer within 5 years				
Non-irrad.	0	47.5	97.3	61.6
Irrad.	5.5	23.8	91.9	52.6
Known survived or dead with cancer after 5 or more years				
Non-irrad.	0	4.7	2.7	2.7
Irrad.	0	4.8	8.1	5.2
Known survived without cancer 5 or more years				
Non-irrad.	100.0	47.6	0	35.6
Irrad.	94.5	71.4	0	42.2
Known survived with or without cancer 5 or more years				
Non-irrad.	100.0	52.4	2.7	38.3
Irrad.	94.5	76.2	8.1	47.4

nodes will survive for five or more years after radical operation alone, and that roentgen irradiation cannot benefit them because all the disease has already been removed.

The results obtained in our Group II irradiated series may be used to illustrate the prognosis from the treatment of patients with localized movable tumors in the breast but with only a few axillary lymph nodes showing metastases. We found in the series having operation alone that almost half (47.6 per cent) were free from demonstrable evidence of cancer and a little more than half (52.4 per cent) still survived five or more years with or without evidence of their disease. When these results are compared with our irradiated Group II cases in which the disease was present to the same extent we find 71.4 per cent are free from demonstrable evidences of cancer and about three-quarters of them (76.2 per cent) are still surviving five or more years with or without evidences of their disease.

It seems justifiable to conclude from this study of our Group II cases that about half the patients with carcinomas localized in the breast but with even a moderate degree of axillary metastases will survive five or more years if operation is the only treatment but, if roentgen irradiation is given after operation, more of them will survive for the same period of time.

This observation about Group II cases is in distinct contrast to the results obtained in the Group I series in which axillary metastases were absent and the prognosis was almost certain cure by operation alone. Apparently the explanation of the benefits from irradiation in the Group II cases is not that more of these patients are definitely cured, but that their lives are prolonged by the treatment. This was proven in a year-to-year study of the survival rates in each of our series. It was found that the percentage of non-irradiated patients surviving in each yearly period after operation alone was about the same as the percentage of irradiated patients surviving in the next succeeding year. This indicated that the treatment extended the average life expectancy of the patients in Group II at least one year.

I have stated that it is not always possible to distinguish between our Groups I and II cases by physical examination alone, one reason being that enlarged axillary nodes are palpable in but few of the Group II cases. This difficulty may be offered as an objection to our scheme for classifying mammary carcinomas. However, I may suggest that often it is just as difficult to distinguish between a benign and a malignant tumor of the breast by physical findings alone, and therefore it is necessary in a great many patients to employ some surgical procedures and microscopic examination to reveal the nature of neoplasm in the breast. Because of this uncertainty, I believe, it is the consensus among surgeons that when a tumor is found in a breast and there is not sufficient clinical evidence to determine whether it is malig-

nant or benign, it should be excised *in toto* for immediate examination microscopically. If the tumor is proved to be benign, no other operation is necessary. If it is malignant, more radical surgical procedure should be performed immediately to remove more tissue, including the axillary contents, because of the uncertainty of the presence of axillary metastases even by the gross examination at operation, and conclusions about the extent of the disease and prognosis must be established after careful microscopic examination of every lymph node.

Therefore it is evident that it is unnecessary from the standpoint of prognostication to distinguish between Group I and Group II cases of mammary carcinoma on the basis of clinical findings alone, because most patients with localized tumors in the breast are subjected to operation anyway, not only in order to determine whether the growth is benign or malignant but to indicate what therapeutic procedures should be instituted; this depends upon whether or not malignant disease has been found to have metastasized to the axillary nodes.

Our Group III cases present a problem entirely different from that in the other two groups. The prognosis for these advanced cases may be determined by noting that not one of our 82 Group III patients comprising both the non-irradiated and irradiated series survived for five years without evidence of disease.

A few of these patients survived five years but still had cancer. It may be that they would have lived as long if nothing whatever had been done for them. It is well known that not all women with mammary carcinomas will die from their disease in five years even if they are not treated. The average natural duration or life expectancy for a woman with mammary carcinoma is thought to be about three years, but a few have been known to live 20 or more years without treatment.

It might appear from this tabulation of five-year survivals that the patients in Group III were not benefited by either operation or irradiation. The question may be answered by determining what happened during the first three years after operation. (Table V). It was found that those lost or dead within six months comprised about one-third (34.1 per cent) of the non-irradiated series and one-tenth (9.7 per cent) of the irradiated series. One might inquire if the difference might be explained on the basis that not so many patients would be lost who continued to come for irradiation treatment from time to time; but this is not the explanation, because only a few of the patients in the non-irradiated series were actually lost in the first six months after operation (7.3 per cent) and most of them (26.8 per cent) were known to be dead, but no patient who received irradiation was lost, and all (9.7 per cent) previously mentioned were known to have died. Therefore, the irradiation even of these patients with advanced disease apparently did prolong some lives as proved again by the other intervals tabulated. This study also brings up the question of

TABLE V.—COMPARISON OF CASES LOST AND THOSE DEAD WITH CANCER IN 41 NON-IRRADIATED GROUP III CASES AND 41 IRRADIATED GROUP III CASES

(Results in Numbers and Percentages)

	1–6 Months		7–12 Months		13–24 Months		24–36 Months	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Lost trace with cancer:								
Non-irrad.	3	7.3	4	9.7	5	12.2	5	12.2
Irrad.	0	0	0	0	0	0	2	4.8
Known died with cancer:								
Non-irrad.	11	26.8	18	43.8	30	73.1	32	78.0
Irrad.	4	9.7	18	43.8	26	63.4	31	75.5
Lost or died with cancer:								
Non-irrad.	14	34.1	22	53.6	35	85.3	37	90.3
Irrad.	4	9.7	18	43.8	26	63.4	33	80.5

whether or not operation did these patients any good or might have done harm to some patients when it is noted that almost half (43.8 per cent) were known to be dead within 12 months and almost three-fourths (73.1 per cent) within two years.

I believe that we are justified in concluding from the study that patients who present the classical evidences of advanced mammary carcinoma, thus placing them in our Group III, are incurable from the standpoint of operation alone, and that radical surgical procedures can do no good but actually may do harm by shortening their lives. And in addition, since irradiation apparently prolonged the lives, even of some of these patients with advanced disease, from three to six months by the comparatively modest quantities that they received five or more years ago, we may conclude that patients with such advanced disease will survive comfortably as long or longer if treated by irradiation alone and if they are not subjected to any radical surgical procedures.

I may say at this time that I have stated that the irradiated patients were treated more than five years ago and that they received very moderate treatment. I need not go into the details of the technic which have been published previously. It is sufficient to state that, by our newer methods of prolonged irradiation which makes it possible to administer a total quantity many times greater than previously, we may anticipate in the future much better results from roentgen treatment alone, or combined with the application of radium, or palliative operations for certain cases.

Having discussed what has been the prognosis and what seem to be the logical methods for treating mammary carcinomas according to the extent of the disease found in different groups of cases, it must be apparent that it is obligatory for clinicians and especially surgeons to try to differentiate by careful physical examinations between early or moderately advanced cases of carcinoma (Group I and Group II) and those that are advanced or incurable by operations (Group III). If this is done and patients with only early or moderately advanced carcinomas (Group I plus Group II) are operated upon, the results from operation alone would be about 60 to 70 per cent five-year survivals. If when patients are found to have carcinomas still localized in the breast but with axillary metastases, they are given irradiation post-operatively, the five-year survival rate will be even greater. But the important problem is to recognize the 50 per cent of patients who have incurably advanced (Group III) carcinomas and not to subject them to radical operative procedures but to treat them by irradiation alone. The clinical manifestations of incurable mammary carcinoma are:

I. Manifestations affecting the skin:
   (*a*) Edema (pig or orange skin) even of moderate degree;
   (*b*) Brawny red induration and inflammation;
   (*c*) Multiple nodules;
   (*d*) Ulceration.
II. Manifestations affecting the breast:
   (*a*) Edema;
   (*b*) Diffuse infiltration;
   (*c*) Multiple secondary tumors;
   (*d*) Fixation of the breast or tumor to chest wall.
III. Manifestations of metastases:
   (*a*) Axillary lymph nodes, numerous, or fixed;
   (*b*) Supraclavicular metastases or edema of the arm;
   (*c*) Distant metastases (lungs, bones, other organs).

CONCLUSIONS

1. A classification for cases of mammary carcinomas is desirable and should be adopted. It should be based upon the clinical and pathological evidences of the extent of the disease.

2. A classification is suggested which divides cases into three groups, each of which is shown to represent different prognosis and indications for therapeutic procedures.

3. The early Group I cases with localized, movable tumors in the breast and without axillary metastases should be operated upon but not irradiated. Almost 100 per cent of these patients will survive for five years. This group comprises about 30 per cent of all cases.

4. The patients in Group II with moderately advanced, localized, movable tumors in the breast and only a few axillary lymph node metastases should have radical, operative removal of as much of the diseased tissue as possible and, in addition, they should be given irradiation post-operatively. About 50 per cent of such patients will survive five years if operation is the only treatment and at least 75 per cent will survive as long if irradiation is given. This group comprises about 25 per cent of all cases.

5. The patients in Group III with clinical manifestations of incurability should not be subjected to radical surgical procedures. No patient will survive for five years without evidence of cancer. These patients should be treated by irradiation alone to prolong their lives. This group comprises about 45 per cent of all cases.

6. A thorough search should be made for the clinical manifestations of incurability which are enumerated, and patients with any of them should not be subjected to a radical operation.

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PRACTICAL METHODS OF REDUCING THE CANCER DEATH RATE[1]

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RADIOLOGY has arisen within the period of years that parallels the development of a renewed interest in the study of cancer. Many have ascribed to radiology the part of having been the determining factor or at least furnishing the urge for the renewal of a practical attack upon cancer. The amount of research work is tremendous. Clinical reports of progress would fill volumes, but it is time certainly for us to apply and to translate into human equations many of these research and clinical facts.

It probably seems too formidable to attempt any practical attack through genetics because we would not accomplish much within our own lifetime, yet there are a great many things we do know that should be applied by all physicians. Surely radiologists should be the leaders in enthusing, translating, promoting, and propagandizing cancer control to the whole profession because radiology has provided some measure of hope and cheer to the cancer problem through radiation therapy and enhanced the surgical attack by roentgen diagnosis.

With the belief that the control and treatment of cancer are professional problems, with the idea of increasing the hopes and ambitions of physicians in early diagnosis and successful cure, and with confidence that the advances in cancer knowledge warrant the banishment of folk-lore fear and professional pessimism, it is interesting to translate some of the statistics and research facts into human equations which will be applicable in the daily practice of all physicians.

Let us erect a declaration of faith in certain basic cancer facts. Let these facts serve as flags which symbolize our faith.

First, *cancer is a preventable disease.* This was brought very forcibly to my attention at one time, and the anecdote may serve to impress this fact. I was sitting next to the great pathologist, Dr. James Ewing, at a dinner and was inviting him to Kansas City to a clinical conference in which we intended to program a "Symposium upon Diseases of Degeneration." Ewing said, "I am not interested at all. I cannot agree that cancer is a disease of degeneration. Better confine your program to heart, kidney, and syphilis because cancer is a preventable disease."

Whenever we put a disease in the preventable category, we then know that we can learn to avoid and control that disease even before we find its cause or its cure.

In this morning's newspaper Muir, the great English authority upon leprosy, reports that leprosy probably will be eradicated entirely from the face of the earth before the cause is found. It may be likewise with cancer. It seems unreasonable to insist that failure to find the cellular, biochemical, parasitical, or chimerical cause of cancer precludes the application of proven measures of prevention, control, and cure.

Let us say that the first flag of our attacking army is that *cancer is a preventable disease.*

Let us take another very simple statement for our second flag. Let us agree that *cancer starts from a single spot,* perhaps unicellular, in tissue or organ. It does not start as a tumor, or ulcer, or grossly invading growth. Such displays are late expressions or developments of the small early lesion that we should have been able to recognize. We must be more suspicious and insist upon proof of the innocence of visible and invisible tissue displays of altered function. Cancers are microscopic before they become palpable or visible. Visible cancers do not produce pain before they are palpable. Many cancers that

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defy direct vision become indirectly visible by roentgen examination.

For the third point, let us rally round the flag symbolizing *chronic or persistent irritation* as the most useful and practical causal element in cancer. The single, repeated, or continuous insults to tissues by seemingly innocent bruises (certain breast cancers); the chronic pyogenic insults (endocervicitis); parasitic insults (actinomycosis); the direct injury by trauma (osteogenic sarcoma); insults by foreign bodies (pipe, betel nut, occupation). The persistent or renewed activity of unwelcome or uninvited congenital tissue remnants; growth-trends and the complicated sequential abnormal tissue reactions outside normal physiology—these may be regarded as irritations or insults to the normal metabolism of cells. Careful history-taking brings out some degree of chronic irritation and organic injury in a large percentage of cancers.

As another divisional flag let us take this: *the early diagnosis and prompt eradication* of the lesion by surgery or radiation therapy will promote a decline in cancer mortality.

Here is a field in which radiology can arrogate to itself a great deal of the progress in cancer diagnosis. We have heard surgeons talk for so many years upon inaccessible cancer—it is accessible cancer when visible or palpable. We should include in that accessible field those types of malignancy which are visible through a simple instrument like a scope. Roentgen examinations serve to make visible those changes in the internal organs which are evidence of a malignant disturbance. In order to visualize an early malignancy in the brain, we use the ventriculogram or encephalogram. In pulmonary tissues before the microscopic evidence is rescued by a bronchoscope, the roentgen examination of the lungs serves to locate the site from which the biopsy is secured.

The directly visible, palpable, and easily biopsied field of cancer includes skin, lip, mouth, throat, and breast. The rectum and vagina are also palpable and become visible directly by the speculum.

The indirectly visible field, or the so-called inaccessible field, includes the brain, lungs, stomach and colon, kidneys, bladder, and bones. The indirect visibility is accomplished by roentgen examinations combined with artificially produced opacity in otherwise homogeneous tissues through biochemical or displacement methods.

Another flag: *biopsy study by pathologists* has displaced the macroscopic evidence of the surgeon. Simple biopsy rescue is possible in all visible and palpable lesions of the skin, lip, mouth, cervix, rectum, or what is distinctly the preventable field of malignancy. The biopsy rescue becomes a more formidable but not impossible measure in breast, brain, larynx, lung, stomach, and colon. There should be more dependence upon the roentgen interpretation of bone malignancy than surgeons seem to afford us.

Another flag: treatment principles are assuming new alignments, depending upon *tumor grading and sensitivity* to radiation. Total surgical excision of cancerous growths is jealously maintained and with a more courageous completeness, but the partial extirpation of any cancer is condemned. Surgical exposure for intimate radium therapy is a valuable venture. The use of well-executed radium therapy for those superficial malignancies to skin, mouth, lip, and cervix has become rather universal, but there must be insistence upon the exhibition of lethal and homogeneous radiation therapy.

The simplicity, comfort, and low expense of radium therapy render it increasingly available throughout the world. Roentgen therapy occupies a distinct field, especially in inoperable and incurable malignancy. It may afford relief from pain and may delay exitus, and it continues as a research problem of gradually increasing merit.

The last flag: that *educational propaganda* be divided between that which is *professional* and that which is *popular*. The professional appreciation of cancer

facts and fancies is far more important than lay education because if physicians are not practising the early diagnosis of cancer, what good does it do to advise potential or inquiring patients to consult their physicians?

These are the flags which symbolize our faith in certain facts regarding cancer. You are all familiar with research facts and clinical facts which support each one of these contentions. We must translate more of these facts to the general profession. It must absorb them. It must use them.

We should look at some old surgical premises with new vision. It has been an accepted policy that a surgeon must be absolutely sure of the presence of mammary malignancy before performing a radical mastectomy. Consequently, the mortality for mammary malignancy remains unnecessarily high. Why not demand some scientific proofs of the innocence or benignity of a breast tumor and sacrifice a few innocent tumors in breasts? Then we will surely have excised all of the malignant ones!

Again, if the cancer facts that we know regarding the development of cancer at the cervix were thoroughly exercised within the practice of every physician, we could cut down the incidence of cervical cancer. If these women were taken care of in their post-natal period in a way that is proper and justifiable; if the irritation to tissues which results from the lacerations and infections were removed, and if we treated adequately the pre-cancerous stage of a malignancy of the cervix, we would avoid the horrible morbidity and mortality of this preventable group of cancers.

I am not at all in favor of the development of huge cancer centers. They are all right in well-populated communities, but they are not going to serve the people all over the country. It is far more practical for us to bring a cancer service to the patient than to insist that the patient must be transported to one specialist or one institution.

If the profession will attack cancer in its early stages, there is not the necessity for these large institutions. If this cancer problem is attacked upon the facts that we now know, you and I will be using our roentgen apparatus for diagnostic purposes rather than for treatment purposes. I can't help but feel that the present tremendous amount of roentgen therapy that is being done for late cancer will be looked back upon some time as just another interesting phase in medical history. *One candle power of intelligence applied in early diagnosis* or in the elimination of the known pre-cancerous situation will be far *better than any million volts of irradiation for late cancer displays.*

At the Battle of Gettysburg a drummer boy too small to fight was carrying the flag. He saw the enemy retreating beyond the line of the company trenches. The soldiers called to him and said, "Hey! Come on back. Bring the flag back to the line!"

But the boy yelled, "No! Bring the line up to the flag!"

THE RELATION OF HEREDITY TO THE OCCURRENCE OF CANCER

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I WISH in the time allotted to me through your generosity to present two phases of the cancer problem, namely, the working out of a very exact mathematical theory which explains to a nicety not only the occurrence but also the localization of cancer in my stocks of mice; and second, to suggest ways in which there could be a practical application of these findings to the human cancer tragedy.

I beg that you will give attention to the charts I shall present and not look upon them as a piece of work of academic interest only, for they show and explain the breeding out of breast cancer through nine generations of mice. This complete elimination of breast cancer from an entire family of mice tested through so many generations, is highly significant when one considers the fact that breast cancer is so overwhelmingly the cancer menace of mice that geneticists and research workers, other than myself, rarely report upon any other form of mouse malignancy. In terms of human life, these nine generations would mean over six hundred years of complete freedom from breast cancer, and the exemption from cancers which I have obtained in some strains of mice throughout the twenty-seven years of this work would, in terms of human experience, mean a freedom from cancer of some three thousand years.

Cancer is not an academic problem maintained for the bickerings of some geneticists who do not happen to agree on this or that detail of the method of cancer heredity. It is a social problem, a vast social menace, and it is time something was done to stop its increase before it moves up to be the first of all death causes. It is to such an end that my work has gone through every storm it has met.

I would say in passing that I have an exhibit which gives the exact data concerning every mouse in the strain here reported, although only a few of the charts can be included herein with their analyses and explanations. I shall be glad to show this exhibit at any time to any one interested therein. Let me first show you the theory.

There are apparently two causes operative in the production of cancer: first, inherited susceptibility (that is, susceptible soil) and second, perhaps, irritation or chronic stimulation by particular hormones or so-called carcinogenic agents, or by trauma, or by other causes of the types fitted to induce it. In mice resistant by heredity, irritations and traumas incident to life in this laboratory have never induced cancer, while in mice susceptible by heredity to only one location of cancer, irritation or stimulation applied to other parts of the body have to date failed to induce neoplasms in these insusceptible tissues.

In some malignancies under study, when irritation to the locally susceptible tissues has been avoided, cancer has not occurred even in susceptible strains. For example, uneven teeth are frequent in mice: consequently they strike upon the soft tissues of the mouth and jaw. This seems to be one of the possible external factors inducing cancer of these tissues. Many mice in cancer-susceptible strains have developed malignancy at the point of contact of such teeth. I have not yet determined whether the crooked teeth or the beginning of cancer is the first cause of this relationship. In carcinoma-susceptible mice the result is carcinoma. In sarcoma-susceptible mice the result is sarcoma. In non-susceptible strains the result is never malignancy, but only inflammatory or septic changes have been found. It has seemed possible also to prevent such cancers in susceptible mice by keeping their teeth short and thus preventing the constant traumatism of these

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soft tissues. The fact that by keeping the teeth short in cancer-susceptible mice it has been possible to prevent these cancers, seems to demonstrate that the "irritation" factor is here of influence as an accelerator or an external causative agent.

I am presenting the report of an entire strain of mice, comprising 650 individuals, derived from the original mating of two individuals, and carefully analyzed by inbreeding for nine generations. The object of this study has been to determine the behavior of malignancy as a biologic character, and to demonstrate the influence and method of heredity in the occurrence of malignancy and in its localization.

I remind you that these tumors are not produced by any experimental procedures whatever. They are all spontaneous tumors, arising naturally in the life of the animals and developing without any interference of any sort, at any time. Every animal is kept in hygienic conditions under controlled diet and temperature. Every mouse is permitted to live out its natural life span and thus to show all of its natural cancer tendencies and all of the systemic changes wrought by cancer. None is killed. Since the first death in this study, every mouse has been autopsied as soon as possible after death and every suspicious tissue has been examined histologically for malignancy. These tissues and slides are all in permanent museum. Every precaution is taken to see that no mouse is destroyed by postmortem changes. To this end, all are examined at least once daily, and every sick mouse three times daily. None has ever been discarded without autopsy. No cancers are reported without confirmed microscopic diagnoses of malignancy. Thus every precaution is taken against these important and very common chances for error.

I wish to remind you also, that whatever reports are made concerning the experimental production of tumors by various agents, there are included in my studies close to 100,000 individual tumors in mice to which nothing has been done. These spontaneous tumors will have to be taken into account in the consideration of any experimentally applied external agent as the efficient cause of cancer.

The theory here offered as an explanation of the mode of cancer inheritance is as follows: (1) Malignancy is an abnormal type of proliferation transmitted as a localized recessive character, each type of malignancy being a unit character and capable of suppression by a dominant allelomorph; that is, one unit recessive character for carcinoma, one unit recessive character for sarcoma, one unit recessive character for leukemic disease. (2) Localization factors as physiologic characters of such a nature that they provide the occasion for malignancy where they occur in tissues by heredity capable of malignancy, and when the necessary interrelation with the external causative factor arises, if such there be.

The causes of cancer then would be: (1) One unit recessive genetic factor for each type of malignancy (carcinoma, sarcoma, leukemic disease), not just one unit character for all types of malignancy. (2) One unit recessive genetic localization factor determining each site of malignancy for the type—mammary gland, or lung, or body-wall, for example. (3) External causative factors perhaps (environmental or intra-organic). (4) Metabolic relationships. (5) Longevity or ability to live into the age for high cancer probability.

Failures in the expected occurrence of cancer may thus be due to:

(1) Failure of assortment between the recessive factor for malignancy and the recessive localizing factor.
(2) Failure of a possible external factor.
(3) Unfavorable metabolic conditions (intercurrent and degenerative diseases).
(4) A short life span.

The symbols used in the theory are as follows—be patient with these so that the charts will be meaningful.

FACTORS FOR MALIGNANCY

I. Epithelial malignancy, a recessive unit character represented by d_1.

II. Connective tissue malignancy, a recessive unit character represented by d_2.

III. Leukemic type malignancy, a recessive unit character represented by d_3.

The dominant allelomorph for each of these recessive characters is represented by the corresponding capital. The possible distribution and combinations of these types would be:

carc : sarc : leuks : carc-leuks : carc-sarc : sarc-leuks : carc-sarc-leuks.

FACTORS FOR LOCALIZATION

I. Epithelial localizing factors: recessive unit characters for lung, l; mammary gland, m; ovary, o. The dominant allelomorphs for these characters are represented by capitals.

II. Connective tissue localizing factors: recessive unit characters for body-wall, b; and subcutaneous, s; with dominant allelomorphs B and S.

III. The localizing factors for leukemic type are not analyzed, due to disagreements in the pathology of these types, and to the frequent apparent merging of one into the other. These factors represent the common sites of malignancy in this strain.

The following are the possible assortments of unit recessive characters for the localization of malignancy. I ask you to attend to this in order to see how difficult it is to prove these things.

I. A two-character assortment (one for malignancy and one for localization): lung carcinoma, d_1l; ovarian malignancy, d_1o; mammary gland carcinoma, d_1m; body-wall sarcoma, d_2b; subcutaneous sarcoma, d_2s.

II. A three-character assortment (one for malignancy and two for localization): for the simultaneous occurrence in the same mouse of carcinoma of the lung and ovarian adenoma or carcinoma, d_1lo; of sarcoma of the body-wall and sarcoma of the subcutaneous tissues, d_2bs.

III. A four-character assortment (two for malignancy and two for localization): for example, the simultaneous occurrence in one mouse of carcinoma of the lung and sarcoma of the body-wall would require the assortment, d_1d_2lb; of carcinoma of the lung and sarcoma subcutaneous, d_1d_2ls; adenoma of the ovary and sarcoma body-wall, d_1d_2ob; of adenoma or carcinoma of the ovary and subcutaneous sarcoma, d_1d_2os.

All four of these sites should be found also assorting with leukemic disease, and this would require the four-recessive assortment for their concurrent appearance. There should then be found mice with both carcinoma of the lung and leukemic disease; sarcoma of the body-wall and leukemic disease; sarcoma of the subcutaneous tissues and leukemic disease; and ovarian adenoma and leukemic disease.

IV. A six-factor assortment which would involve the occurrence in one mouse of carcinoma, sarcoma, and leukemic disease. This would require at least the assortment of six recessive characters, three for malignancy (that is, one for each type of malignancy) and three for localization (that is, one for each location). All of these difficult combinations must be found for the validation of this theory. An examination of the totals for the entire line will show that all of these combinations were found.

Where the genetic pattern for the concurrent appearance of these characters is very complicated, that is, in a mouse with many forms of malignancy, it will readily be seen that the necessary assortment of these characters is rare, by the laws of chance. Not only is the genetic pattern complex, but the added complexity of the inter-relation with possible external causative factors, and the age incidence for the different types of tumor, make them combinations difficult to obtain. The only considerable failures in my totals lie in these complex categories. And in spite of these difficulties all of these combinations required for the validation of the theory were found.

Note that this complicated genetic pattern for the occurrence of multiple types and sites of malignancy in the same mouse does not complicate the genetic pattern of breast carcinoma, for example, any more

than would the occurrence of chronic nephritis in the same mouse with breast carcinoma. Carcinoma remains unit recessive; breast location remains unit recessive. Nor does it complicate the genetic pattern for sarcoma or for leukemic disease, both of which remain unit recessive. The complex genetic pattern applies to the occurrence of breast carcinoma and body-wall sarcoma, for example, in the same mouse, which would give a genetic pattern of four unit recessives, one for carcinoma, one for the breast, one for sarcoma, one for the body-wall, and so on, for the combination of different types and sites of malignancy in the same mouse.

Line 7 is one of 10 crosses made between red females from one strain, and albino males from an unrelated strain. The entire experiment involves between 4,000 and 5,000 mice. The females were sisters from a strain *carrying a low percentage of malignancy*. Of these malignancies, 20 per cent were mammary gland carcinoma, 66.6 per cent were leukemic disease, and 6.7 per cent were mixed tumors of the thyroid. The ancestral lines that lay behind the strain from which these females came showed lung tumor, ovarian tumor, and subcutaneous tumors, but no body-wall tumors in any of its branches.

The parent males were brothers from a strain *carrying a high percentage of malignancy*. Of these malignancies, 16 per cent were carcinoma of the mammary gland, 38.7 per cent were carcinoma of the lung with a few carcinomas in other organs, 25.8 per cent were sarcomas chiefly in the body-wall and subcutaneous tissues; 22.5 per cent were leukemic disease.

The parent females were obviously able to transmit the localization factors for each of the various sites shown in the hybrid crosses, with the exception of body-wall, a tumor site that appears nowhere in any of their ancestral strains. The localization factor for body-wall was carried in by the males. As body-wall malignancy nowhere appeared in the F_1 in any of the 10 hybrid crosses, the parent females evidently carried only the dominant allelomorph and were not responsible for the localization of body-wall malignancy in the hybrid strains. In Line 7, 32.9 per cent of all its malignancy was body-wall sarcoma.

Line 7 was orginated by a red female with carcinoma of the mammary gland crossed with an unrelated albino male dying of pneumonia, without cancer. There was only one offspring from this cross, a female dying of pleuritis at an advanced age, without cancer. Mated back with her father to make the strain, she produced a line carried through nine generations, which neither in F_1 nor in any of the succeeding generations ever produced a carcinoma of the mammary gland or any other tumor of the mammary gland. Whereas, when the same female was mated with a male from Line 1, which carried a rather high percentage of mammary gland carcinoma, the F_1 showed mammary gland carcinoma, and breast cancer persisted throughout the three generations from that cross. The parent male from Line 1 would seem responsible for the introduction of mammary gland carcinoma. There is no evidence here of an extra-chromosomal influence, either in breast cancer or any other form of malignancy.

Age must be taken into consideration in all these genetic studies. The test age, 17 months, was established for this Line 7, which is six months lower than the average age for malignancy in this very long-lived line. That is, all mice living to the age of 17 months are included in the findings. The average age for the occurrence of ovarian adenoma and carcinoma, lung carcinoma, and sarcoma of the body-wall and subcutaneous tissues, was so high that the test age of 19 months was established in estimating the probabilities for these types of malignancy. All mice showing cancer are included in the findings. The only non-cancerous mice excluded are those dying under test age. The average non-cancer age of the mice included in the findings was 22.5 months; the average cancer age was 22.3 months, nearly identical.

Only 12.2 per cent of the females died

under test age, so that most of them were subjected to the test of age and were able to demonstrate their genetic potentialities. Of the males, however, 42.8 per cent died under test age, of fighting and septic wounds, so that nearly half of the males were eliminated from the age test, and undoubtedly many potentially cancerous males were eliminated in this considerable slaughter in early life. For the theory 81 NC ♀ and 71 NC ♂ were possible for the entire line of 650, or 152 NC. The findings for the tested 477 mice gave 155 NC, or a failure of malignancy in only three mice for complete accord with my theory.

In the summary of the assortment of malignancy and the characters for the localization of malignancy, the findings for carcinoma and sarcoma showed no shortage of tumors for the theory in mice living into test age. (*See Charts.*)

CHART 87

LINE 7, F_1

		Malignancy factors	Localization factors*
Parents	par ♀ (90501) carc.m.gl 14 mo. 11 da.	$d_1D_2D_3$ $d_1D_2D_3$	m L O B S m L o B s
	par ♂ : pneumonia (86725) 10 mo. 27 da.	$D_1D_2D_3$ $d_1\ d_2\ d_3$	M l O b S M l O b S

* The localization factors for leukemic type are not included in the analyses because of disagreements in the pathology of these types.

No. offspring 1 ♀ dying at 19 mo. 1 da. of sup. myocarditis, pericarditis, pleuritis
No. in findings 1 ♀

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (1:1)	NC :	Carc
For 1	.5	.5
Findings for 1	1	0

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 1	FINDINGS
carc. m.gl (d_1m)	0	0
carc. lung (d_1l)	0	0
adenoma ovary (d_1o)	0	0
sarc. body-wall (d_2b)	0	0
sarc. subcut. (d_2s)	0	0
Three recessives (1 for malignancy: 2 for localization).		
m.gl-lung (d_1ml)	0	0
m.gl-ovary (d_1mo)	0	0
lung-ovary (d_1lo)	0	0
bw-sub (d_2bs)	0	0
Four recessives (2 for malignancy: 2 for localization) carc-sarc*		
m.gl-bw (d_1d_2mb)	0	0
m.gl-sub (d_1d_2ms)	0	0
ov-bw (d_1d_2ob)	0	0
ov-sub (d_1d_2os)	0	0
lung-bw (d_1d_2lb)	0	0
lung-sub (d_1d_2ls)	0	0

* The probabilities for carc-leuks and sarc-leuks are not estimated.

This F_1 ♀ (102374) was classified as genetic carc. with dominant localization factors for the epithelial malignancies. She was heterozygous to sarc. and leuks.

$d_1D_2D_3$ M L O B S
$d_1\ d_2\ d_3$ m l o b s

This F_1 ♀ (102374) had one back-cross litter by her father; this litter was inbred to form Line 7, Br. I, II, and III. She was later bred with an F_1 ♂ from Line 1 forming Line 7y x 1 y^4. The first generations of these two crosses are compared. It is noteworthy (1) that ♀ 90501 with breast carcinoma crossed with ♂ 86725 produced no breast carcinoma; (2) that her daughter 102374 crossed with her father ♂ 86725 produced a family which inbred for nine generations and, yielding 344 females, never showed breast carcinoma; (3) that this same female 102374 outbred with a male from a family showing breast carcinoma produced another family in which breast carcinoma occurred in the F_1 and persisted through three inbred generations.

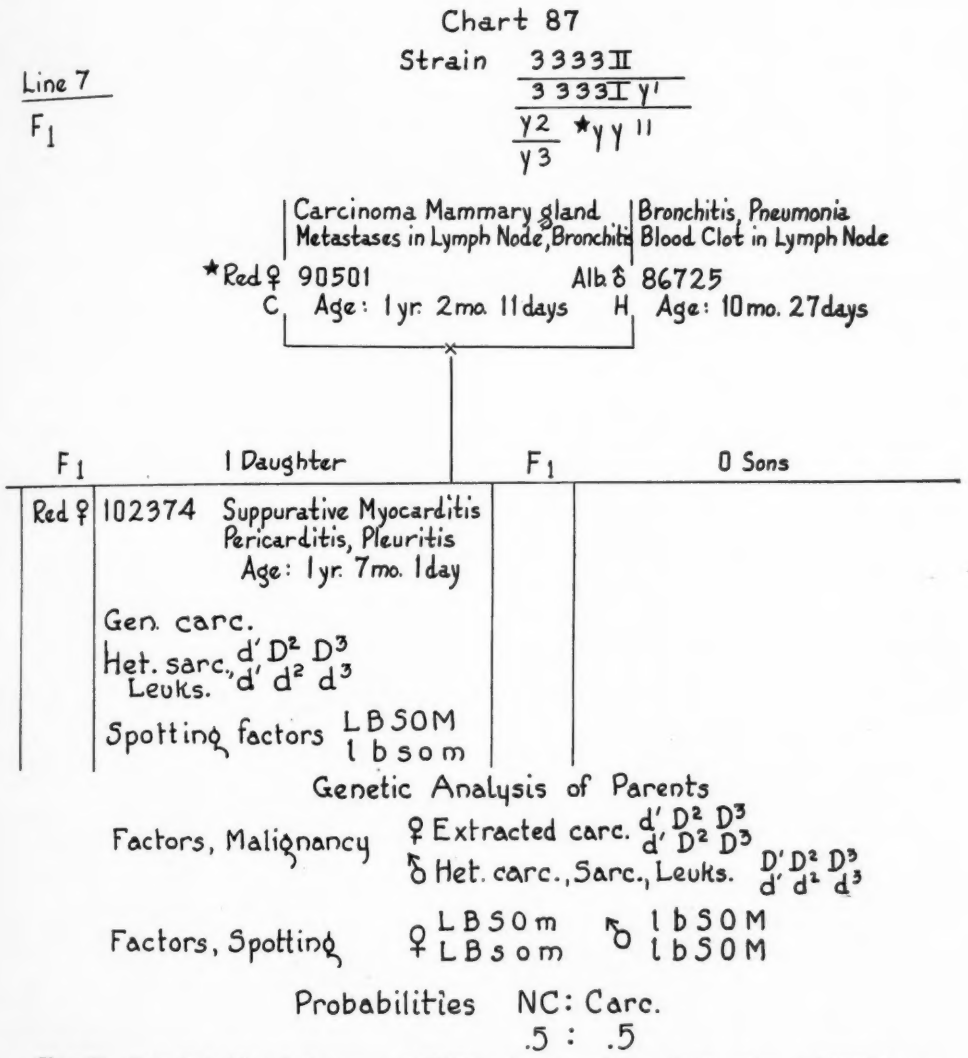

Chart 87. Note that although the parent ♀ 90501 has breast carcinoma, the daughter, ♀ 102374, has no breast cancer. The tendency to the breast as location for carcinoma is here negated by the dominant allelomorphs, MM, carried in by the parent ♂ 86725.

The findings are in accord with the probabilities for the theory.

The formulæ for both malignancy and localization of ♀ 90501, ♂ 86725, and ♀ 102374 are shown.

CHART 88

LINE 7, F_2

		Malignancy	Localization
Parents	F_1 ♀ (102374) pleuritis 19 mo. 1 da. (gen. carc)	$d_1D_2D_3$ $d_1\ d_2\ d_3$	M L O B S m l o b s
	par ♂ (her father) pneumonia 10 mo. 27 da. (86725)	$D_1D_2D_3$ $d_1\ d_2\ d_3$	M l O b S M l O b S

No. offspring 7 4 ♀ : 3 ♂ (2 NC ♀ dead under age)
No. in findings 5 2 ♀ : 3 ♂

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (9:23)	NC	C	
For 7	1.9692	5.0324	
For 5	1.4067	3.5949	
Findings for 5	1	4	♀ 1:1 ♂ 0:3

Prob.	NC	Carc	Sarc	Leuks	C-L	C-S	S-L	C-S-L
For 7	1.9692	1.9692	.6564	.6564	.6564	.6564	.2188	.2188
For 5	1.4067	1.4067	.4689	.4689	.4689	.4689	.1563	.1563
Findings for 5	1	2	1	1				

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy 1 for localization).

	PROB. 7, 4 ♀	PROB. TEST AGE	FINDINGS	
m.gl	0	0	0	
lung (3:1)	1.75	1.25	2	
ovary	0	0	0	
body-wall (7:1)	.875	.625	1	
subcut.	0	0	0	
	2.625	1.875	3	
Four recessives (2 for malignancy: 2 for localization).				
lung-bw (31:1)	.2188	.1563	0	

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	3.5	2.5	2	
sarc	1.75	1.25	1	
leuks	1.75	1.25	1	
	7	5	4	Short 1

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	1.75	1.25	2	
sarc	.875	.625	1	
	2.625	1.875	3	Short 0

Chart 88

Strain $\frac{3333\,II}{3333\,I\,y^1}$ $\frac{y2}{y3}$ ★yy II

Line 7

F_2 Back Cross of F_1 ♀ 102374 with her father ♂ 86725

Suppurative Myocarditis
Pleuritis, Pericarditis

Bronchitis, Pneumonia
Blood Clot in Lymph Node

F_1 Red ♀ 102374 Gen. C Age: 1 yr. 7 mo. 1 day × Parent Alb. ♂ 86725 H Age: 10 mo. 27 days

Sp. cell sarc. of mes., intes., ovaries, kidney, uterus, pancr., liver, muscles, lymph nodes — 4 Daughters

F_2			F_2		
★Red ♀	107201 Br. I	2 Sp. cell Sarcomas Body Wall Age: 1 yr. 9 mo. 8 days	★Red ♂	108430 Br. I	Carcinoma Lung Hemorrhage in Mediastinum Age: 1 yr. 10 mo. 19 days
Bl. ♀	94677 Br. II	Acute Colitis, Appendicitis Fatal Hem. from Thoracic Aorta Age: 8 mo.	★Alb. ♂	106292 Br. II	Leukemia Age: 1 yr. 8 mo. 9 days
Alb. ♀	100703 Br. III A	Colitis, Peritonitis Age: 1 yr. 2 mo. 10 days	★Alb. ♂	113166 Br. III A.B	Carcinoma Lung Hemorrhage in Lung Age: 2 yr. 5 mo. 11 days
Alb. ♀	108024 Br. III B	Chronic Nephritis Age: 1 yr. 10 mo. 4 days	Red ♂	Dead in infancy	

	NC	:	C
Prob. for 7	1.9692	:	5.0324
Prob. for 5	1.4067	:	3.5949
Findings for 5	1	:	4

Chart 88. Note that when F_1 ♀ 102374 is mated back with her father 86725 no breast cancer occurs in the offspring. Nor did it ever occur again in this Line 7 made by the back-cross of 103274 with her father 86725, although this line was carried through nine generations and numbered 650 mice. The findings are in accord with the probabilities for the five mice living to test age.

Obviously no cross was ever made between two mice heterozygous to breast location; that is, both mice carrying $\frac{M}{m}$ in the genetic formula.

CHART 107

LINE 7y x ly⁴, F_1

		Malignancy factors	Localization factors
Parents	par ♀ from Line 7, F_1 sup. pleuritis 19 mo. 1 da. (gen. carc) (102374)	$d_1D_2D_3$ $d_1\ d_2\ d_3$	M L O B S m l o b s
	par ♂ : Line 1, F_1 pseudoleukemia 26 mo. 6 da. (gen. sarc) (110567)	$D_1d_2d_3$ $d_1d_2d_3$	M L O B S m l O b s

No. offspring	23	14 ♀ : 9 ♂ (3 NC ♀ : 4 NC ♂ died under age)
No. in findings	16	11 : 5 (16 in test age probabilities)
Theory	NC : C 1 : 7	

Distribution of malignancy (factors for malignancy considered alone).

Probabilities	NC	:	C	
For 23	2.875		20.125	
For 16	2		14	
Findings for 16	4		12	♀ 3:8 ♂ 1:4

Prob.	NC	:	Carc	:	Sarc	:	Leuks	:	C-L	:	C-S	:	S-L	:	C-S-L
For 23	2.875		2.875		2.875		2.875		2.875		2.875		2.875		2.875
For 16	2		2		2		2		2		2		2		2
Findings for 16	4		3		4		4		0		1		0		0

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy : 1 for localization).

	PROB. 23, 14 ♀	PROB. TEST AGE	FINDINGS
m.gl (7:1)	1.75	1.375	1
lung (7:1)	2.875	2	3
ovary	0	0	0
body-wall (7:1)	2.875	2	2
subcut. (7:1)	2.875	2	3
	10.375	7.375	9
Three recessives (1 for malignancy: 2 for localization).			
lung-m.gl (31:1)	.4375	.3438	0
lung-ov	0	0	0
bw-sub (31:1)	.7188	.5	0
	1.1563	.8438	
Four recessives (2 for malignancy: 2 for localization).			
m.gl-bw (63:1)	.2188	.1719	0
m.gl-sub (63:1)	.2188	.1719	1
lung-bw (63:1)	.3594	.25	0
lung-sub (63:1)	.3594	.25	0
	1.1564	.8438	1

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc (d_1)	11.5	8	4	
sarc (d_2)	11.5	8	5	
leuks (d_3)	11.5	8	4	
	34.5	24	13	Short 11

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	4.625	3.375	4	
sarc	5.75	4	5	
	10.375	7.375	9	Short 0

Chart 107

Line 7y x 1y^4

Strain $\frac{3333\,II}{3333\,I\,y^1}$

F_1 $\frac{y2}{y3}$ $*yy^{11}$

Suppurative Pleuritis
Pericarditis, Myocarditis (Wounds) | Pseudoleukemia

F_1 Red ♀ 102374 — Line 7 Gen. C — Age: 1yr. 7mo. 1day

× Gen. Sarc.-Leuks

*F_1 Bl. ♂ 110567 — Line 1 C — Age: 2yr. 2mo. 6days

F_1		14 Daughters	F_1		9 Sons
Red ♀	103083	Pulmonary Infection Age: 1yr.	*Alb. ♂	100737	Pseudoleukemia Age: 1yr. 23days
*Alb. ♀	103541	Lymphatic Leukemia Age: 1yr. 4mo. 2days	Alb. ♂	103432	Chronic Nephritis Age: 1yr. 1mo. 15days
*Alb. ♀	109110	Pseudoleukemia Age: 1yr. 7mo. 15days	Red ♂	104466	Chronic Nephritis Hemorrhagic Appendicitis Colitis Age: 1yr. 3mo. 21days
Alb. ♀	109798	Chronic Nephritis Age: 1yr. 8mo. 10 days	* Bl. ♂	108717	Sp.cell Sarcoma Subcut. invading Arm Age: 1yr. 8mo. 3 days
Red ♀	110619	Pulmonary Infection Age: 2yr.	*Red ♂	110802	Multiple Carcinomas Lungs Age: 2yr. 7days
*Alb. ♀	111836	Spindle cell FibroSarcoma of Abdominal Wall Age: 2yr. 1mo. 24 days	Bl. ♂	110872	Chronic Nephritis Age: 1yr. 9mo. 27days
*Alb. ♀	111841	Spindle cell Sarcoma of Abdominal Wall Metastases in Lymph Node Age: 2yr. 16days	*Alb. ♂	110897	Pseudoleukemia Age: 1yr. 8mo. 23days
*Blue ♀	111885	Subcut. Spindle cell FibroSarcoma Age: 1yr. 10mo. 7days	Red ♂	108238	Acute Nephritis (Wounds) Age: 1yr. 6mo. 10days
Red ♀	106347	Pneumonia, Abscess in Inguinal Musc. Age: 1yr. 15 days	Alb. ♂	Lost	At age: 3 mo. 1day
*Red ♀	114327	Carcinoma Lungs, Metas. & Hemorrhage in Lungs Age: 1yr. 11mo. 7days			
*Red ♀	113767	2 Carcinomas Lungs Fatal Hemorrhage in Lung Age: 1yr. 10mo. 12days			
Bl. ♀	99417	UnKnown Infection Age: 6 mo. 10 days			
Alb. ♀	116149	Intestinal Infection Age: 2yr. 4mo. 23days			
* Bl. ♀	115389	Sp. cell Sarcoma Subcut. Carcinoma Mammary Gland Age: 2yr. 26da.			

	NC : C
Prob. for 23 -	2.875 : 20.125
(of test age) Prob. for 17 -	2.125 : 14.875
Findings for 17 -	5 : 12
♀ -	3 : 8
♂ -	2 : 4

Chart 107. But note that when the same F_1 ♀ 102374 was hybridized with ♂ 110567 that came from Line 1 which carried breast cancer, breast carcinoma occurred in the first hybrid generation in ♀ 115389. Breast carcinoma persisted in this hybrid Line 7y x 1y^4 throughout its entire course. The male was here responsible for the occurrence of breast cancer. There is a shortage of only 2.8 malignancies.

CHART 89

LINE 7, Br. I F_2

		Malignancy	Localization
Parents	F_2 ♀ : 2 sarc. body-wall mult. sarc. abd. organs 21 mo. 8 da. (107201)	$D_1d_2D_3$ $d_1\ d_2\ d_3$	M L O b S m l o b s
	F_2 ♂ : carc. lung 22 mo. 19 da. (108430)	$d_1D_2D_3$ $d_1\ d_2\ d_3$	M l O B S M l o b s

No. offspring 10 7 ♀ : 3 ♂ (3 NC ♂ dead under age)
No. in findings 7 7 ♀ (4 lived from 19–27 mo.)

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (3:13)	NC	C
For 10	1.875	8.125
For 7	1.311	5.681
Findings for 7	1	6

Prob.	NC	Carc	Sarc	Leuks	C-L	C-S	S-L	C-S-L
For 10	1.875	1.875	1.875	.625	.625	1.875	.625	.625
For 7	1.311	1.311	1.311	.437	.437	1.311	.437	.437
Findings for 7	1	0	3	2	0	0	0	1

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 10, 7 ♀	PROB. TEST AGE	FINDINGS
m.gl	0	0	0
lung (3:1)	2.5	1	0
ovary (7:1)	.875	.5	1
bw (3:1)	2.5	1.5	2
subcut (7:1)	1.25	.75	2
	7.125	3.75	5
Three recessives (1 for malignancy: 1 for localization).			
lung-ovary (15:1)	.4375	.25	0
bw-sub (15:1)	.625	.25	0
	1.0625	.5	
Four recessives (2 for malignancy: 2 for localization).			
lung-bw (15:1)	.625	.25	0
lung-sub (31:1)	.3125	.125	0
ov-bw (31:1)	.2188	.125	0
ov-sub (63:1)	.1094	.0625	1
	1.2657	.5625	1

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	5	2	1
sarc	5	3	4
leuks	2.5	1.75	3

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	3.375	1.5	1
sarc	3.75	2.25	4

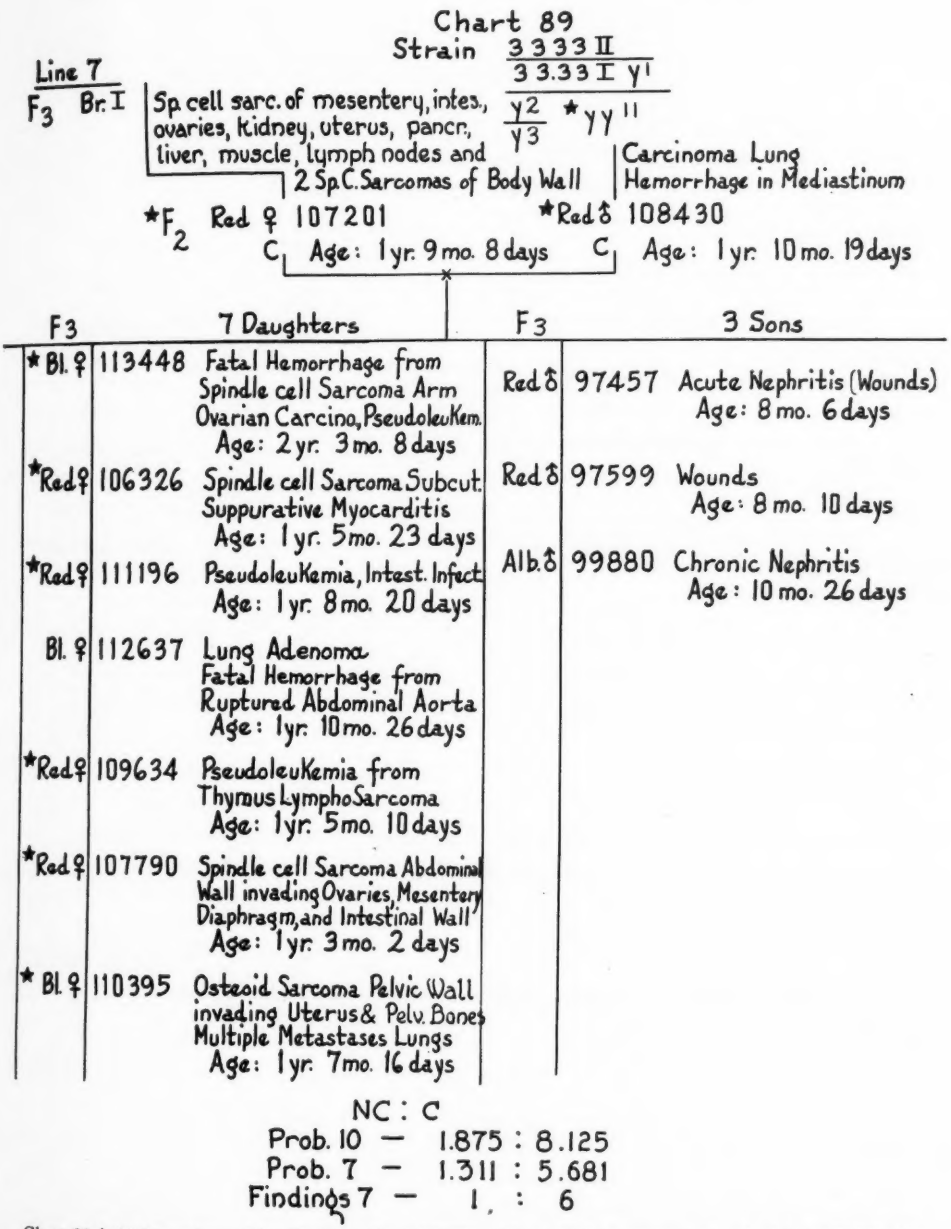

Chart 89 (which continues Line 7) shows F_2 ♀ 107201 with multiple sarcomas, mated with ♂ 108430 with carcinoma of the lung. Note that there is sarcoma and carcinoma in the F_3 offspring, but no breast carcinoma. The findings for malignancy are in exact accord with the probabilities for the theory.

CHART 93

LINE 7, Br. II, F_4 A

		Malignancy	Localization
Parents	F_3 ♀ : carc. lung 25 mo. 21 da. (gen. leuks) (113770)	$d_1D_2d_3$	M I O B S
		$d_1D_2d_3$	M I O b s
	F_3 ♂ : pseudoleuk. 8 mo. (97060)	$D_1D_2d_3$	M L O b S
		$d_1\ d_2\ d_3$	M I O b s
		(suppression of sarc. by dom. allelomorphs)	

No. offspring 8 5 ♀ : 3 ♂ (2 NC ♂ dead under age)
No. in findings 6 5 ♀ : 1 ♂ (2 lived into late test age)

Distribution of malignancy (factors for malignancy considered alone).

Probabilities	NC	C
For 8	0	8
For 6	0	6
Findings for 6	0	6

Prob.	NC	carc	leuks	carc-leuks	
For 8	0	0	4	4	
For 6	0	0	3	3	
Findings for 6	0	1	5	0	(4 of the leuks. died under the age for carc. lung)

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 8, 5 ♀	PROB. TEST AGE	FINDINGS
m.gl	0	0	0
ovary	0	0	0
lung (3:1)	2	.5	1
bw	0	0	0
sub.	0	0	0
	2	.5	1

No probabilities for 3 and 4 recessive assortments.

Summary of malignancy factors (for malignancy considered alone), based on no. of individuals.

carc	4	1	1	
sarc	0	0	0	
leuks	8	6	5	
	12	7	6	Short 1

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	2	.5	1	
sarc	0	0	0	
	2	.5	1	Short 0

Chart 93

Strain $\frac{3333\,II}{3333\,I\,y^{1}}$

$\frac{y2}{y3}$ $\star yy^{11}$

Line 7
F_4 Br. II
A

	Carcinoma Lung, Senile Atrophy	Pseudoleukemia from Thymus Lymphosarcoma
$\star F_3$	Alb. ♀ 113770	$\star$Bl. ♂ 97060
	C Age: 2yr. 1mo. 21 days	C Age: 8mo.

F_4	5 Daughters		F_4	3 Sons	
$\star$Alb. ♀	97139	Thymus Lymphosarcoma becoming Pseudoleukemia Age: 4 mo. 11 days	$\star$ Bl. ♂	100402	Thymus Lymphosarcoma becoming Pseudoleukemia Age: 7 mo. 25 days
$\star$ Bl. ♀	99790	Thymus Lymphosarcoma Ovarian Lymphosarcoma becoming Pseudoleukemia Age: 7 mo. 4 days	Alb. ♂	100584	Intestinal Infection Age: 8 mo.
			Alb. ♂	101009	Pulmonary Infection Age: 8 mo. 16 days
$\star$ Bl. ♀	113208	2 Carcinoma Lungs Age: 1 yr. 11 mo. 6 days			
$\star$ Bl. ♀	109112	Pseudoleukemia Age: 1 yr. 5 mo. 10 days			
$\star$Alb. ♀	115862	Pneumonia Pseudoleukemia Age: 2 yr. 3 mo. 10 days			

	NC : C
Prob. 8	0 : 8
(of test age) Prob. 6	0 : 6
Findings 6	0 : 6

Chart 93. Here F_3 ♀ 113770, with carcinoma of the lung, is mated with ♂ 97060, with pseudoleukemia. Here there are two different types of malignancy mated. Note that leukemic diseases and lung carcinoma occur in the offspring, but there is no breast carcinoma. The findings are in exact accord with the probabilities.

CHART 98

LINE 7, Br. II F_4 F

		Malignancy	Localization
Parents	F_3 ♀: carc. lung 24 mo. 10 da. (gen. sarc) (114871)	$d_1d_2D_3$ $d_1d_2d_3$	M l O B S M l o b s
	*F_3 ♂: benign adenomatous hyperplasia lung; pneumonia 27 mo. 1 da. (116467)	$D_1D_2D_3$ $d_1\ d_2\ d_3$	M L O B S m l o b s

* Benign hyperplasia of the lung is not counted among the malignancies.

No. offspring 26 11 ♀: 15 ♂ (3 NC ♀: 3 NC ♂ dead under age)
No. in findings 20 8 ♀: 12 ♂ (all 20 in late test age)

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (3:13)	NC	C	
For 26	4.875	21.125	
For 20	3.75	16.25	
Findings for 20	4	16	♀ 1:7 ♂ 3:9

Prob.	NC	Carc	Sarc	Leuks	C-L	C-S	S-L	C-S-L
For 26	4.875	4.875	4.875	1.625	1.625	4.875	1.625	1.625
For 20	3.75	3.75	3.75	1.25	1.25	3.75	1.25	1.25
Findings for 20	4	8	5	1	1	1		

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 26, 11 ♀	PROB. TEST AGE	FINDINGS	
m.gl	0	0	0	
lung (3:1)	6.5	5	9	
ovary (7:1)	1.375	1	2	
bw (7:1)	3.25	2.5	3	
sub (7:1)	3.25	2.5	3	
	14.375	11	17	(over-assortment of lung carc)

Three recessives (1 for malignancy: 2 for localization).

lung-ov (15:1)	.6875	.5	1	
bw-sub (31:1)	.8125	.625	1	
	1.5	1.125	2	

Four recessives (2 for malignancy; 2 for localization) carc-sarc.

lung-bw (31:1)	.8125	.625	0	
lung-sub (31:1)	.8125	.625	0	
ov-bw (63:1)	.1719	.125	1	
ov-sub (63:1)	.1719	.125	0	
	1.9688	1.5	1	

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	13	10	10	
sarc	13	10	6	
leuks	6.5	2.5	2	
	32.5	22.5	18	Short 4.5

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	7.875	6	11	
sarc	6.5	5	6	
	14.375	11	17	Short 0

Line 7
F_4 Br II
F

CHART 98

Strain 3333 II / 3333 Iy¹ / y^2/y^3 ★yy"

F_3 C: ★Bl.♀ 114871 — Carcinoma Lung — Age: 2 yr. 10 da.

H: Bl.♂ 116467 — Mult. Adenomas Lungs, Pneumonia — Age: 2 yr. 3 mo. 1 da.

F_4		11 Daughters	F_4		15 Sons
★Alb.♀	116652	Ovarian Adenoma, Lung Aden., 2 Sp. cell Sarcomas Abd. Wall, Perirenal and Lung Metas. Age: 2 yr. 9 da.	★Bl.♂	116775	Carcinoma Lung Age: 2 yr. 15 da.
			★Bl.♂	118417	Sp. cell Sarc. Seminal Ves. Lung Adenoma Age: 2 yr. 3 mo. 6
★Bl.♀	119320	Sp. cell Sarc. Pelvic Wall and left Hind Leg Age: 2 yr. 4 mo. 22 da.	★Bl.♂	119221	Carcinoma Lung Age: 2 yr. 5 mo. 12 da.
★Alb.♀	119455	Ovarian Adenoma, Ca. Lung Age: 2 yr. 4 mo. 27 da.	Bl.♂	119614	Chronic Nephritis Age: 1 yr. 4 mo. 22 da.
Bl.♀	110826	Intest. Infection, Peritonitis Age: 3 mo. 1 da.	★Bl.♂	125399 ①	Carcinoma of Lung Age: 2 yr. 1 mo. 20 da.
Alb.♀	117790 ③ ⑨	Intestinal Infection, Jaundice Age: 1 yr. 1 mo. 26 da.	★Bl.♂	125375	Carcinoma of Lung Age: 2 yr. 2 mo. 27 da.
Bl.♀	117820 ⑪	Intestinal Infection, Jaundice Age: 1 yr. 3 mo. 12 da.	Bl.♂	111813	Intestinal Infection Age: 1 yr. 1 mo. 14 da.
Alb.♀	124812 ②	Intestinal Infection Age: 2 yr. 2 mo. 11 da.	Alb.♂	122769 ②	Rupture Thoracic Aorta Age: 1 yr. 9 mo. 24 da.
★Alb.♀	123164 ④ ⑧	Carcinoma of Lung Age: 1 yr. 7 mo. 18 da.	Alb.♂	120244 ③ ⑤	Acute Neph., Myocarditis Age: 1 yr. 3 mo. 14 da.
★Bl.♀	121694 ⑤	Subcut. Sp. cell Sarcoma Age: 1 yr. 8 mo. 9 da.	★Bl.♂	127640 ④	Early Pseudo Leukemia Age: 2 yr. 5 mo. 2 da.
★Bl.♀	123095 ⑥	Ca. Lung, Lymph. Hyperplasia Age: 1 yr. 10 mo. 10 da.	Bl.♂	124192 ⑥	Intestinal Infection Age: 1 yr. 11 mo. 17 da.
★Bl.♀	124368 ⑦	Carcinoma of Lung Age: 2 yr. 23 da.	★Alb.♂	129790 ⑦	Sp. cell Sarc. Thoracic Wall Age: 2 yr. 9 mo. 16 da.
			Bl.♂	123746	Suppurative Wounds Age: 1 yr. 10 mo. 21 da.
			★Bl.♂	126312 ⑨	Ca. Lung and Base of Teeth Age: 2 yr. 4 mo. 7 da.
			★Bl.♂	126153	Sp. cell Sarc. of Face and Jaw Age: 2 yr. 1 mo. 24 da.

NC : C

Prob for 26 - 4.875 : 21.125

(of test age) Prob. for 20 - 3.75 : 16.25

Findings for 20 - 4 : 16

♀ - 1 : 7

♂ - 3 : 9

Chart 98. Here F_3 ♀ 114871, with carcinoma of the lung, is mated with ♂ 116467 with multiple benign adenomas of the lung. The results show that benign lung adenomas did not show the genetic behavior of a malignancy as such a cross should have given 100 per cent lung malignancy. The findings here are in exact accord with the probabilities of the theory, namely, 4 NC:16 C. There is no breast carcinoma.

CHART 101

LINE 7, Br. II F, F_6 (3) II

		Malignancy	Localization
Parents	F_5 ♀: adenoma ovary 24 mo. 22 da. (130764)	$d_1D_2D_3$	M L o b S
		$d_1 d_2 d_3$	M l o b s
	F_5 ♂: subcut. sarc. (126269) 15 mo. 3 da.	$D_1d_2D_3$	M l O B s
		$d_1 d_2 d_3$	M l o b s

No. offspring 18 9 ♀: 9 ♂ (3 NC ♂ dead under age)
No. in findings 15 9 ♀: 6 ♂ (13 in late test age)

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (3:13)	NC	:	C	
For 18	3.375		14.625	
For 15	2.8125		12.1875	
Findings for 15	4		11	♀ 2:7 ♂ 2:4

Prob.	NC	:	Carc	:	Sarc	:	Leuks	:	C-L	:	C-S	:	S-L	:	C-S-L
For 18	3.375		3.375		3.375		1.125		1.125		3.375		1.125		1.125
For 15	2.8125		2.8125		2.8125		.9375		.9375		2.8125		.9375		.9375
Findings for 15	4		6		3		0		0		1		1		0

(1 sarc. prostate)

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 18, 9 ♀	PROB. TEST AGE	FINDINGS	
m.gl	0	0	0	
lung (3:1)	4.5	3.25	6	
ovary (3:1)	2.25	2.25	3	
bw (3:1)	4.5	3.25	2	
sub (3:1)	4.5	3.25	1	
	15.75	12	12	(over-assortment carc. lung)

Three recessives (1 for malignancy: 2 for localization).

lung-ov (7:1)	1.125	1.125	0	
bw-sub (7:1)	2.25	1.625	1	
	3.375	2.75	1	

Four recessives (2 for malignancy: 2 for localization).

lung-bw (15:1)	1.125	.8125	1	
lung-sub (15:1)	1.125	.8125	1	
ov-bw (15:1)	.5625	.5625	0	
ov-sub (15:1)	.5625	.5625	0	
	3.375	2.75	2	

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	9	7.5	7	
sarc	9	7.5	5	
leuks	4.5	3.75	1	
	22.5	18.75	13	Short 5.75

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	6.75	5.5	7	
sarc	9	6.5	5	
	15.75	12	12	Short 0

Line 7 — Chart 101 — Strain $\frac{3333\,II}{3333\,1y^{1}}$ $\frac{}{Y^{2}/Y^{3}\ \star YY^{II}}$

F_6 Br. II F_6 ③ II

F_5 ★Alb.♀ C: Adenoma Ovary, 130764, Age: 2yr. 22da. — ★Alb.♂ C: Subcut. Sarc., Pneumonia, 126269, Age: 1yr. 3mo. 3da.

F_6		9 Daughters	F_6		10 Sons
★Alb.♀	131017	Adenoma Ovary, Age: 1yr. 10mo. 11da.	Alb.♂	127694	Aden. Lung, Pleuritis, Pericarditis, Age: 1yr. 3mo. 6da.
Alb.♀	131323	Pneumonia, Age: 1yr. 7mo.	Alb.♂	128310	Chronic Neph., Subcut. Abscess, Age: 1yr. 4mo. 15da.
★Alb.♀	131335	Sp. cell Sarc. Abd. Wall, Hem. Ovaries, Age: 1yr. 11mo.	★Alb.♂	129121	Carc. Lung - Intest. Infec., Age: 1yr. 6mo. 11da.
★Alb.♀	132521	Carcinoma Lung - Hem. Ovaries, Age: 2yr. 18da.	Alb.♂	129210	Intestinal Infection, Age: 1yr. 5mo. 20da.
Alb.♀	133135	Hem. Ovaries, Intest. Infec., Jaundice, Age: 1yr. 10mo. 16da.	★Alb.♂	129325	2 Carcinomas Lung, Age: 1yr. 5mo. 26da.
★Alb.♀	133333	Sarc. of Abd. & Thor. Walls & Diaphr., Age: 2yr. 2mo.	Alb.♂	128924	Adenoma Lungs, Age: 1yr. 1mo. 25da.
★Alb.♀	133391	2 Subcut. Sarc. Thoracic Wall, Pseudo leukemia, Hem. Ovary, Age: 2yr. 18da.	★Alb.♂	130511	Sp. cell Sarc. Prostate involving Rect, Urinary Retention, Uremia, Age: 1yr. 5mo. 8da.
★Alb.♀	133744	Carcinoma Lung, Age: 2yr. 1mo. 9da.	★Alb.♂	131432	Carc. Lungs, Metas. Lungs, Age: 1yr. 6mo. 11da.
★Alb.♀	133861	Sarc. left Abd. Wall & both Hind Legs, Hem. Ovary, Carcinoma Lung, Age: 1yr. 11mo. 27da.	Alb.♂	133219	Pulmonary Infection, Age: 1yr. 9mo. 25da.

	NC	:	C
Prob. for 18 -	3.375	:	14.625
(of test age) Prob. for 15 -	2.8125	:	12.1875
Findings for 15 -	4	:	11

	NC	:	C
♀	2	:	7
♂	2	:	4

Chart 101. Here F_5 ♀ 130764, with malignant adenoma of the ovary, is mated with ♂ 126269, with subcutaneous sarcoma. Sarcomas, adenomas, and leukemic diseases occur in the offspring, but there is no breast carcinoma. This also is a cross between two types of malignancy, and the fact that we do not get 100 per cent of malignancy demonstrates that there is one unit recessive factor for carcinoma (or adenoma) and another unit recessive factor for sarcoma. The results show a shortage of only 1.18 malignancies for perfect accord with the theory.

CHART 103

LINE 7, Br. II F, F_5 (4)

		Malignancy	Localization
Parents	F_4 ♀ : carc. lung 19 mo. 18 da. (123164)	$d_1D_2D_3$	M l O b S
		$d_1\ d_2\ d_3$	M l o b s
	F_4 ♂ : pseudoleuk. 29 mo. 2 da. (127640)	$D_1D_2d_3$	M L o b s
		$d_1\ d_2\ d_3$	M l o b s

No. offspring 14 8 ♀ : 6 ♂ (3 NC ♂ dead under age)
No. in findings 11 8 ♀ : 3 ♂ (8 in late test age) 6 ♀ : 2 ♂

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (3:13)	NC	C	
For 14	2.625	11.375	
For 11	2.0625	8.9375	
Findings for 11	5	6	♀ 3:5 ♂ 2:1

Prob.	NC	Carc	Sarc	Leuks	C-L	C-S	S-L	C-S-L
For 14	2.625	.875	.875	2.625	2.625	.875	2.625	.875
For 11	2.0625	.6875	.6875	2.0625	2.0625	.6875	2.0625	.6875
Findings for 11	5	1	1	3	0	1		

(2 leuks died under age for carc)

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 14, 8 ♀	PROB. TEST AGE	FINDINGS
m.gl	0	0	0
lung (3:1)	3.5	2	1
ovary (3:1)	2	1.5	1
bw (3:1)	3.5	2	2
sub (7:1)	1.75	1	1
	10.75	6.5	5
Three recessives (1 for malignancy: 2 for localization).			
lung-ov (7:1)	1	.75	0
bw-sub (7:1)	1.75	1	1
	2.75	1.75	1
Four recessives (2 for malignancy: 2 for localization).			
lung-bw (15:1)	.875	.5	0
lung-sub (31:1)	.4375	.25	0
ov-bw (15:1)	.5	.375	1
ov-sub (31:1)	.25	.1875	1
	2.0625	1.3125	2

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	7	4	2	
sarc	3.5	2	2	
leuks	7	4	3	
	17.5	10	7	Short 3

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	5.5	3.5	2	
sarc	5.25	3	3	
	10.75	6.5	5	Short 1.5

Line 7
F_5 Br. II

Chart 103

Strain 3333 II
3333 Iy^1
Y^2/Y^3 ★YY^{11}

F_4 ★Alb.♀ 123164 — Carcinoma Lung
Age: 1yr. 7mo. 18da.

★Bl.♂ 127640 — Pulmonary Infec. Early Pseudoleuk.
C
Age: 2yr. 5mo. 2da.

F_5		8 Daughters	F_5		6 Sons
★Alb.♀	127620	Leukemia Age: 1yr. 2mo. 4da.	Bl.♂	127315	Abscess Lung - Supp. Wounds, Hyperplastic Spleen Age: 1yr. 2mo. 5da.
★Alb.♀	129296	Pseudoleukemia Age: 1yr. 5mo. 23da.	Alb.♂	127325	Wounds, Acute Nephritis Age: 1yr. 3mo. 28da.
★Alb.♀	129926	Reticulum-Cell Sarcoma Liver Age: 1yr. 7mo. 22da.	★Bl.♂	127990	Carcinoma Lung Age: 1yr. 5mo. 10da.
Alb.♀	130189	Intestinal Infection Acute Dilatation of Stomach Age: 1yr. 8mo. 10da.	Alb.♂	128841	Pulmonary Infection Intestinal Infection Age: 1yr. 5mo. 14da.
★Alb.♀	130538	Fibro-Sarc. Abd. Wall, Pneumonia Age: 1yr. 9mo. 4da.	Bl.♂	129907	Acute Neph., Urinary Reten. Age: 1yr. 7mo. 21da.
Bl.♀	132289	Pulmonary Infection Age: 2yr. 3da.	Alb.♂ I	123241	Intestinal Infection Age: 2mo. 14da.
★Alb.♀	133428	Sarc Pelvic Wall and Hind Leg Intra-Abd. Sarc., Adenoma Ovary Age: 2yr. 2mo. 5da.			
Bl.♀ I	131698	Chronic Nephritis Age: 1yr. 8mo. 18da.			

	NC : C
Prob. for 14	2.625 : 11.375
(of test age) Prob. for 11	2.0625 : 8.9375
Findings for 11	5 : 6
♀	3 : 5
♂	2 : 1

Chart 103. Here is another cross between two different types of malignancy: F_4 ♀ 123164, with carcinoma of the lung, mated with ♂ 127640, with pseudoleukemia. Here again different recessive genes control carcinoma and pseudoleukemia, respectively, since we do not get 100 per cent malignancy from such a cross. The findings are only 2.9 malignancies short for the theory. Leukemias, carcinoma, and sarcoma occur as expected, but there is no breast carcinoma.

CHART 110

LINE 7, Br. II $\frac{E}{F}$, F_6 I

		Malignancy	Localization
Parents	F_5 ♀: mult. osteo-sarc. body-wall 27 mo. 3 da. (125001)	$D_1d_2D_3$ $d_1\ d_2\ d_3$	M L o b S M l o b S
	F_5 ♂: carc. lung 32 mo. 18 da. (127477)	$d_1D_2D_3$ $d_1\ d_2\ d_3$	M l o B S M l o b s

No. offspring 28 18 ♀: 10 ♂ (4 ♀ : 1 ♂ dead under age)
No. in findings 23 14 ♀: 9 ♂ (21 in late test age) 12 ♀: 9 ♂

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (3:13)	NC	C	
For 28	5.25	22.75	
For 23	4.314	18.694	
Findings 23	4	19	♀ 2:12 ♂ 2: 7

Prob.	NC	Carc	Sarc	Leuks	C-L	C-S	S-L	C-S-L
For 28	5.25	5.25	5.25	1.75	1.75	5.25	1.75	1.75
For 23	4.314	4.314	4.314	1.438	1.438	4.314	1.438	1.438
Findings 23	4	11	2	1	1	4		

(1 carc. jaw)

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 28, 18 ♀	PROB. TEST AGE	FINDINGS
m.gl	0	0	0
lung (3:1)	7	5.25	6
ovary (1:1)	9	6	9
bw (3:1)	7	5.25	6
sub.	0	0	0
	23	16.5	21
Three recessives (1 for malignancy: 2 for localization).			
lung-ov (3:1)	4.5	3	0
Four recessives (2 for malignancy: 2 for localization) carc-sarc.			
lung-bw (15:1)	1.75	1.313	0
ov-bw (7:1)*	2.25	1.5	4
	4	2.813	4

* If this probability is based on the entire fraternity there is no over-assortment.

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	14	10.5	16	
sarc	14	10.5	6	
leuks	7	5.25	2	
	35	26.25	24 (over-assortment of carc)	Short 2.25

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	16	11.25	15	
sarc	7	5.25	6	
	23	16.5	21	Short 0

Line 7 $\frac{E}{F}$ I

$\frac{F_6 \text{ Br II}}{}$

Chart 110

3333 II

Strain 3333 Iy'

$Y^{s}/_{Y^{3}}$ ★ YY''

F_5 ★Bl.♀ 125001 C | Mult. Osteo Sarcomas Dorsal & Vent. Thor. Walls, Ribs & Pleura | ★Bl.♂ 127477 C | Carc. Lungs

Age: 2yr. 3mo. 3da. | Age: 2yr. 8mo. 18da.

F_6	17 Daughters		F_6	10 Sons	
★Bl.♀	118790	Thymus Lympho sarc. becoming Pseudoleuk. Age: 9mo. 13da.	Alb.♂	123908	Chronic Nephritis Age: 1yr. 2mo. 14da.
Bl.♀	124582	Acute Neph., Urinary Reten., Hyp. Heart Age: 1yr. 4mo. 18da.	★Bl.♂	126699	Carcinoma of Lung Age: 1yr. 11mo. 16da.
Bl.♀	125125	Pneumonia, Hem. Ovaries Age: 1yr. 4mo. 22da.	★Bl.♂	126272	Anaio-Sarc. Thoracic Wall, Fatal Hem. Age: 1yr. 10mo. 24da.
★Bl.♀	125785	Abscess Lungs, Adenom. Uterus & Ovary Age: 1yr. 7mo. 4da.	★Bl.♂	127916	Sq.cell Ca. Base of Teeth invading Bone Age: 2yr. 2mo. 11da.
★Alb.♀	126720	Carcinoma of Lung Age: 1yr. 5mo. 28da.	Bl.♂	127658	Acute Nephritis, Urinary Retention Age: 1yr. 9mo. 18da.
Bl.♀	122212	Pulmonary Infection Age: 10mo. 20da.	★Bl.♂	128395	2 Carcinomas Lung Age: 1yr. 11mo. 6da.
★Bl.♀	127760	Bilateral Adenomas of Ovaries Age: 1yr. 11mo. 16da.	Bl.♂	130591	Cort. cell Adenoma Adrenal, Chr. Neph Age: 2yr. 3mo. 28da.
★Bl.♀	127352	Adenoma Ovary, Chronic Nephritis Age: 1yr. 10mo. 20da.	★Bl.♂	130847	Multiple Carcinomas Lungs Age: 2yr. 2mo. 28da.
★Bl.♀	128403	R.C.-Sarc. Abd. Wall, Adenoma Ovary Age: 2yr. 21da.	★Bl.♂	131241	Ca. Lung, Metas. Lungs, Adenom. Lung Age: 2yr. 7mo. 1da.
★Bl.♀	128405	Adenoma & Hemorrhage Ovary Age: 2yr. 21da.	★Bl.♂	132614	Carcinomas Lungs Age: 2yr. 5mo. 23da.
Bl.♀	128491	Supp. Nephritis, General Infection Age: 1yr. 9mo. 2da.			
★Bl.♀	129691	Sp.cell Sarc. Pelvic Wall, Aden. Ovary, Pneum. Age: 2yr. 6mo. 3da.			
★Bl.♀	129742	Sp.cell Sarc. Abd. Wall, Adenoma Ovary Age: 2yr. 6mo. 6da.			
★Alb.♀	130780	Sp.cell Sarc. Rt. Abd Wall and Hind Leg 2 Sp.cell Sarc. Inner Aspect Thoracic Wall Age: 2yr. 2mo 22da.			
Bl.♀	124584	Hemorrhage Ovaries Age: 1yr. 4mo. 18da.			
★Bl.♀	127162	Endothel. Sarc. Liver, Spleen, Neck Nodes Bilateral Adenomas Ovaries Age: 1yr. 10mo. 7da.	★Alb.♀	127487	2 Sp.cell Sarc. Abd. Wall, Mult. Lung Metas., Bilat. Adenomas Ovaries Age: 2yr. 1mo. 14da.

	NC	:	C
Prob. for 28 -	5.25	:	22.75
(of test age) Prob. for 23 -	4.314	:	18.694
Findings for 23 -	4	:	19
♀ -	2	:	12
♂ -	2	:	7

Chart 110. Again a cross is made between two different types of malignancy; F_5 ♀, with multiple sarcomas in multiple sites, and ♂ 127477, with lung carcinoma. Again the expectation is not 100 per cent malignancy, but instead a ratio of 4 NC:19 C. The findings are in exact accord with the expected ratio. Sarcomas, carcinomas, and leukemic diseases occur in the offspring, but again there is no breast carcinoma.

CHART 117

LINE 7, Br. II $\frac{E}{F}$, F_6 VII

		Malignancy	Localization
Parents	F_5 ♀: int. inf. 17 mo. 21 da. (123152)	$D_1D_2D_3$ $d_1\ d_2\ d_3$	M L o b S m l o b s
	F_5 ♂: multiple carc. lungs 33 mo. 3 da. (130401)	$d_1D_2D_3$ $d_1\ d_2\ d_3$	M l o b s M l o b s

No. offspring 21 12 ♀: 9 ♂ (3 NC ♂ dead under age)
No. in findings 18 12 ♀: 6 ♂ (17 in late test age)

Distribution of malignancy (factors for malignancy considered alone).

Probabilities (9:23)	NC	:	C	
For 21	5.9067		15.0949	
For 18	5.0625		12.9375	
Findings for 18	6		12	♀ 3:9 ♂ 3:3

Prob.	NC	:	Carc	:	Sarc	:	Leuks	:	C-L	:	C-S	:	S-L	:	C-S-L
For 21	5.9067		5.9067		1.9689		1.9689		1.9689		1.9689		.6563		.6563
For 18	5.0625		5.0625		1.6875		1.6875		1.6875		1.6875		.5625		.5625
Findings for 18	6		6		2		1		1		1		0		1

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: for localization).

	PROB. 21, 12 ♀	PROB. TEST AGE	FINDINGS
m.gl	0	0	0
lung (3:1)	5.25	4.25	4
ovary (1:1)	6	6	6
bw (3:1)	5.25	4.25	4
sub (7:1)	2.625	2.125	2
	19.125	16.625	16

Three recessives (1 for malignancy: 2 for localization).

lung-ov (3:1)	3	2.75	1
bw-sub (7:1)	2.625	2.125	2
	5.625	4.875	3

Four recessives (2 for malignancy: 2 for localization).

lung-bw (15:1)	1.313	1.063	0
lung-sub (31:1)	.6563	.5313	0
ov-bw (7:1)	1.5	1.375	2
ov-sub (15:1)	.75	.6875	1
	4.2193	3.6568	3

Summary of malignancy (factors for malignancy considered alone), based on no. of individuals.

carc	10.5	9	9	
sarc	5.25	4.5	4	
leuks	5.25	4.5	3	
	21	18	16	Short 2

Summary of localization (assortment of malignancy and localization factors), based on no. of tumors.

carc	11.25	10.25	10	
sarc	7.875	6.375	6	
	19.125	16.625	16	Short .625

Line 7 — Chart 117 — 3333 II

$\frac{F_6\ Br.II}{F\ VII}$ $\frac{E}{F}$

F_5 Bl.♀ Het. NC | Intest. Infection 123152 Age: 1yr. 5mo.

★Bl.♂ 130401 Carc. | Mult. Ca. Lungs Age: 2yr. 9mo. 3da.

Strain 3333 IY^1 Y^2/Y^3 ★YY II

F_6	12 Daughters		F_6	6 Sons	
★Bl.♀	123364	Aden. Ovary with Fatal Hem. Age: 1yr. 2mo. 21da.	Bl.♂	127090	Intestinal Infection Age: 1yr. 8mo. 17da.
Bl.♀	126395	Intest. Infection, Jaundice Age: 1yr. 7mo. 3da.	Bl.♂	127459	Supp. Wounds, Supp. Myocard. Age: 1yr. 7mo. 18da.
★Bl.♀	126674	Ca. Lungs, Metas., Bilat. Aden. Ovaries Age: 1yr. 9mo. 17da.	★Bl.♂	128110	Carcinoma Lung Age: 1yr. 9mo. 22da.
★Bl.♀	126802	Sp. cell Sarc. Abd. Wall, Intra Abd. Exten Age: 1yr. 9mo. 28da.	★Bl.♂	130212	Pseudo Leukemia Age: 2yr. 1mo. 16da.
★Bl.♀	127307	Carcinoma Lungs Age: 1yr. 11mo. 3da.	Alb.♂	130794	Appendicitis, Colitis Age: 2yr. 3mo. 14da.
★Bl.♀	127490	Lymphosarc. Stom., Panc, Kidneys. Adenoma Ovary Age: 1yr. 11mo. 11da.	★Alb.♂	133475	Ca. Lungs, Cyst Aden. Subcut. Age: 2yr. 8mo. 2da.
★Bl.♀	127854	Aden. Ovary with Fatal Hemorrhage Age: 1yr. 8mo. 13da.			
★Alb.♀	128505	Sp. cell Sarc. Thor. & Abd. Walls & 2 Subcut.", Bilat. Aden. Ovaries, Pseudo leukemia. Age: 2yr. 18da.			
Bl.♀	129707	Intestinal Infection Age: 2yr. 10da.			
★Bl.♀	129716	Sp. cell Sarc. Thor. Wall and Arm Adenoma Lung. Hem. Ovary Age: 2yr. 2mo. 4da.			
Alb.♀	130364	Intestinal Infection Age: 2yr. 3mo. 19da.	★Alb.♀	130012	Sp. cell Sarc. Thor. & Abd. Walls Aden. Ovary, Pneumonia Age: 2yr. 3mo. 23da.

(of test age)	NC	:	C
Prob. for 21 -	5.9067	:	15.0949
Prob. for 18 -	5.0625	:	12.9375
Findings for 18 -	6	:	12
♀ -	3	:	9
♂ -	3	:	3

Chart 117. Here heterozygous non-cancer ♀ 123152 (her father was genetically carcinomatous) is mated with ♂ 130401, with multiple lung carcinomas. Sarcoma, carcinoma, and leukemic disease occur, but there is no breast carcinoma.

The findings are in exact accord with the expectation for the theory. Throughout these charts there is no evidence of an extra-chromosomal factor for breast cancer, which was ruled out in the first generation by the dominant allelomorphs for localization in the breast carried in by the ♂ (shown in the first chart here presented).

These charts show the necessity for considering not only a malignancy factor but also a localization factor. The small shortage of malignancy when malignancy factors only are considered, is eliminated when the assortment of localization factors with malignancy factors is considered. There is thus no shortage whatever of cancer occurrence for the entire Line 7 of 650 mice.

TOTALS LINE 7, F_{1-6}

		Malignancy factors	Localization factors
Parents	par ♀ : carc.m.gl 14 mo. 11 da. (90501)	$d_1D_2D_3$ $d_1D_2D_3$	m L O B S m l o B s
	par ♂ : pneumonia 10 mo. 27 da. (86725)	$D_1D_2D_3$ $d_1\ d_2\ d_3$	M l O b S M l O b S

No. of mice 650 (344 ♀ : 306 ♂) 173 NC dead under test age 42 ♀ : 131 ♂
No. in findings 477 (302 ♀ : 175 ♂)

Average NC age 22.5 mo. ♀ : 22.5 mo. ♂ 22.5 mo. range 17–30 mo.
Average C age 22.3 mo. ♀ : 21.6 mo. ♂ 23 mo. range 4–33 mo.

Distribution of malignancy (factors for malignancy considered alone).

Probabilities	NC	C		
For 650	151.8245	498.2235		
For 477	106.8741	370.1259		
Findings for 477	155	322	♀ 70	232
			♂ 85	90

Probabilities	NC	Carc	Sarc	Leuks	C-L	C-S	S-L	C-S-L
For 650	151.8245	125.7617	103.1313	59.5665	55.6289	89.3185	34.5021	30.3145
For 477	106.8741	90.6881	77.4375	42.4372	40.6252	69.1253	26.125	23.6876
Findings for 477	155	129	74	39	11	55	5	8

(1 teratoma omitted)

The conspicuous failures are in the multiple type groups which require the assortment of 4 and 6 recessive factors (2 or 3 for malignancy and 2 or 3 for localization).

Localization of malignancy (assortment of malignancy and localization factors); 2 recessives (1 for malignancy: 1 for localization).

	PROB. 650, 344 ♀	PROB. TEST AGE	FINDINGS	SHORT
m.gl (d_1m)	0	0	0	
lung (d_1l)	174.0625	124.0625	123	
ovary (d_1o)	96.125	81.875	95	
body-wall (d_2b)	144.125	103.5	106	
subcut. (d_2s)	83.688	60.25	62	
	498.0005	369.6875	386	0
Three recessives (1 for malignancy: 2 for localization)				
lung-ovary ($d_1$lo)	55.4688	48.0938	16	
bw-subcut. ($d_2$bs)	48.5951	32.5626	31	
	104.0639	80.6564	47	33.6564

The most conspicuous failure in the assortment of any group was in lung-ovary (sex incidence).

Four recessives (2 for malignancy: 2 for localization) carc-sarc.				
lung-bw ($d_1d_2$lb)	41.7837	31.1266	19	
lung-sub ($d_1d_2$ls)	22.5018	16.8913	7	
ov-bw ($d_1d_2$ob)	28.8439	24.5781	39	
ov-sub ($d_1d_2$os)	14.8987	13.1798	19	
	108.0281	85.7758	84	1.7758

The probabilities for ov-bw and ov-sub are based on the number of females. If these probabilities were based on the entire group there would have been no over-assortment.

Summary of malignancy (malignancy factors considered alone).		Based on no. of individuals.	
carc (d_1)	302.75	210.5	203
sarc (d_2)	255.5	185.75	142
leuks (d_3)	178.25	125.5	63
	736.5	521.75	408 113.75

This considerable shortage of tumors in mice living into test age, indicates the presence of another genetic factor assorting with the malignancy factor. This second recessive character is the factor for localization.

Summary of localization (assortment of malignancy and localization factors).		Based on no. of tumors.	
carc (d_1)	270.1875	205.9375	218
sarc (d_2)	227.813	163.75	168
	498.0005	369.6875	386 0

To summarize: The strain from which the parent female came was a *low percentage malignancy strain.* Of the tumors carried, it was relatively high in carcinoma of the mammary gland, very high in leukemic disease. There was neither ovarian adenoma nor sarcoma frankly shown in the parent female strain.

The strain from which the parent male came was a *high percentage malignancy strain.* Of the tumors carried, it was relatively low in mammary gland carcinoma.

only one-third as high a percentage of leukemic disease as in the female strain, high in lung carcinoma, low in ovarian adenoma, and high in sarcoma.

The resulting hybrid strain of 650 mice, was a *high percentage malignancy line*, high in lung carcinoma, very high in sarcoma, high in ovarian tumors, relatively low in leukemic disease (nearly identical in percentage with the male strain), and with no mammary gland carcinoma whatever throughout nine generations of individually tested mice. There was throughout the whole range of malignant types tested no evidence of an extra-chromosomal factor.

These charts and figures demonstrate beyond doubt that types and sites of malignancy are segregating out, and hence that the tendency to malignancy and to its localization is inheritable. The actual findings given from every type of cross made, and the theory presented explain the facts and ratios of these findings so exactly that there is no shortage whatever in the number of malignancies, which is in complete accord with the theory.

I call your attention to the page of totals for the entire Line 7, of which only a few fraternities could be charted in this paper.

The parent female 90501 and the parent male 86725 are given with their formulæ both for malignancy and for localization. There were 477 mice that lived into test age. The average age of non-cancer mice was 22.5 months, identical for females and males. The average age of cancer mice was 22.3 months, for females 21.6 months and for males 23 months. Note the long range of age incidence in malignancy, from 4 to 33 months, due to the very early occurrence of some cases of leukemic disease.

The probabilities for 477 mice were 106.87 NC : 370.12 C; the findings were 155 NC : 322 C. This shortage of 48 cancerous individuals (when malignancy factors alone are considered) shows the necessity for a localization factor also to explain the findings.

For the validation of the theory it is necessary that there should be carcinoma, sarcoma, and leukemic disease, together with every possible combination of these forms of malignancy. Note that all of these combinations did occur.

The probabilities and findings for 477 were:

	NC	Carc	Sarc	Leuks
Probabilities	106.8741	90.6881	77.4375	42.4372
Findings	155	129	74	39

	C-L	C-S	S-L	C-S-L
Probabilities	40.6252	69.1253	26.125	23.6876
Findings	11	55	5	8

This is very striking when one considers that the chance to get the six recessive combinations, carc-sarc-leuks, of which there were eight in Line 7, varied from a 7 : 1 chance to a 255 : 1 chance, according to the type of matings made.

Note that throughout this line of 650 mice there is no breast cancer although the parent female, 90501, actually had breast cancer. There is no indication here of any extra-chromosomal factor. Neither is there any basis for considering malignancy as a dominant, since if one considers malignancy alone without the localizing factors there is a shortage of 7.5 carcinomas, 43.75 sarcomas, and 62.5 leukemic diseases, or a total shortage of 113.75 tumors, even for a recessive.

Note that when malignancy alone was considered there was a shortage of 48 cancerous individuals, but when the assortment of malignancy factors with localization factors was the basis of the analysis, there was no shortage whatever and the findings were in perfect accord with the theory of: one unit recessive for carcinoma; one unit recessive for sarcoma; one unit recessive for leukemic disease, and one unit recessive for each location of malignancy. This requires the assortment of all these factors, each with the others, when all of these factors are bred in, as was the case in Line 7 here presented.

It seems to me that, so far from completely homozygous material being necessary for the solution of the genetics of cancer, such homozygous material could not

find the solution. For when the only form of malignancy in a stock is breast carcinoma, then malignancy occurs only in the breast and only in the epithelium, and these two factors for malignancy and for localization thus seem to be one factor, because they always occur together, and it is misleading. But with material of this sort, homogeneous in that only certain types and sites of malignancy ever occur, but heterogeneous in that it carries more than one type and site of malignancy, then these combinations do occur, which make it possible to explain the genetics of cancer. This material shows every possible combination of the unit character for each type of malignancy, with every other type of malignancy, and with every unit character for localization. It seems to show that malignant growth of each type differs in only one gene from non-malignant growth of that type, since the figures are accurate only for malignancy and localization as unit recessives. For malignancy and localization, as unit recessives, the figures are nearly perfect.

This material in its heterogeneous content of malignancy, parallels human material in cancer occurrence, and this theory which I have demonstrated is submitted as a probable explanation of the genetics of human cancer.

All geneticists actually working in cancer agree that there is a hereditary basis in malignant disease. Indeed, so finally is this accepted that much of modern cancer research is based upon this fact, and strains of mice of different cancer susceptibility are now known to be necessary for such studies. Many of the outstanding members of the medical profession, radiologists, surgeons, dermatologists, and internists do accept this fact of cancer susceptibility. It is time to do something about it.

This brings me to the practical aspect of this work. What shall we do? I have been telling that for over sixteen years, and Karl Pearson, of England, before me, repeatedly made the same plea—that is, the plea for human records. I am here to make that plea again and to remind you that the necessity for human records is the same, irrespective of any details of a genetic theory; indeed, they would in time prove the correctness or the error of any genetic theory, and they would be the court of last appeal.

I have spoken to this body of men and women many times, and your reception of me and of my work has been most cordial, but you also have done nothing about it, while cancer, of which you handle thousands upon thousands of cases, has finally come to be in second place of all death causes.

Like the others, you perhaps think we can do nothing to breed out cancer. Before Pasteur's work was accepted, and before Florence Nightingale's work was done, nobody thought there was any such truth about infections which placed them within control, and everybody scoffed at aseptic wounds and hospitals. Now these things are commonplaces and have become routine procedures. I am willing to admit that any step actually to breed out cancer may lie far ahead, but the glory will be to those who actually do it. And when it is done, it also will be routine procedure. If specific types and sites of tumor can be ruled out of mouse families, they can be ruled out of human families. In Line 7, carcinoma of the mammary gland, though bred in by the parent female, was eliminated in the first generation and permanently eliminated from the lives of nine generations thereafter, involving in the main line and its hybrid derivatives over a thousand tested females.

We can make possible this future procedure by the simple method of taking adequate records now, and assembling them in a central bureau where they can be of service.

There is, moreover, a matter in which these records will be of immediate value, and in which you yourself can use them. They will be of immeasurable and immediate diagnostic value. In the laboratory where the ancestry and the immediate family of every mouse is on record, it is possible to predict the probable causes of

death in each member of any family with a very small margin of error. A study of human records, such as I am suggesting, would show the attending specialist, first, the probable type of diseases to be expected in a family, due to ancestry; second, the meaning of symptoms, sometimes fatally hard to ascribe to their cause, but which have been presented before in the family; third, the probable reaction to types of treatment, and fourth, the probable prognosis. These things I can predict in my mice from knowledge of the family records.

This pre-knowledge of probable diseases, reactions, and prognosis within a family would, I think, if it were universally at the command of practitioners, revolutionize medicine, since we should then not only know something about the disease and its treatment of choice, but we should also know something about the patient.

DISCUSSION OF SYMPOSIUM

DR. FRANCIS CARTER WOOD (New York City): I am happy to discuss Dr. Portmann's paper because I think it represents a great advance in our classification of malignant growths of the breast from a practical aspect—one which will lead to the collection of statistics which are of value.

Unless we proceed with such classifications as this and all workers publish their records co-ordinating their cases just as Dr. Portmann suggests and as he has done himself, we will have the continuation of the sort of statements which you can hear from any group of surgeons. For instance, most of them say that x-ray has been proved to be of no value post-operatively, entirely disregarding the large volume of statistics which are available from Germany.

Our own American statistics in general have not been properly collected, the cases have not been properly co-ordinated, the x-ray has been of varying types, and unless we can get a standard not only in classification, as Dr. Portmann suggests, but also a classification and standardization of the type of radiation which is to be done on these cases in which radiation is necessary, we will never have a type of information which will enable us to advise the individual patient as to what should be done.

I quite agree with him that the pathologic classifications are of small value because grouping and studies of the morphology of cells are of little value to the individual. They tell what a hundred patients will do but they do not tell what the individual will do.

We know, for instance—always have known, in fact—that the gelatinous type of carcinoma is less malignant in a general sense than the scirrhous type and yet we all see patients with carcinomas of the gelatinous type die with great ease despite microscopic analysis, which shows that the tumor should be cured by operation. On the other hand, we do know that these gelatinous types are not susceptible to radiation.

The classification of Dr. Portmann, it seems to me, is the best of the lot. It should be adopted in some official way. The College of Surgeons, you know, is printing forms on which records are to be made so as to avoid loose history-taking and to see that all the facts are recorded, and I think we might well do the same thing with Dr. Portmann's plan. It is unquestionably the best that has been published so far.

There are still debatable matters, which Dr. Portmann himself raises. Shall we consider every case with small pig-skin area as inoperable? I don't agree that it is. Nor do I always agree that we should not operate upon an ulcerating carcinoma. If the case is to be palliated with the greatest effectiveness, it is sometimes necessary to remove a large ulcerating breast simply without opening the axilla, close the wound as quickly as possible, and then begin post-operative radiation. That may restore the patient to a condition in which she can go back to her normal activities for a year or two.

Such people almost inevitably die, but there is a palliative surgery which, if you can get it done simply and quickly, enables a person to carry on when it is perfectly im-

possible for her to do so otherwise. It also relieves the patient of the expense of dressings and the offensive odor which comes from such an ulcerating surface.

There is still a question as to how long these individuals' lives are prolonged, but I have a feeling that removal of the infectious material prolongs the patient's life somewhat and that radiation will prevent an immediate return.

There is another point, and that is we must do everything to ensure that our pathologic diagnoses are good. The College of Surgeons has forced upon the country a scheme which hospitals are not prepared to meet—that they must have a pathologist. Pathologists are scarce—good ones very much so—and it is quite astonishing to consider the number of incorrect diagnoses which are going on in the country, made by pathologists who are not properly trained.

There is need also for the careful checking of some of our doubtful types of tumors by experts, not trusting finally to a local pathologist's diagnosis.

DR. WRIGHT CLARKSON (Petersburg, Va.): I want to express my appreciation for the privilege of discussing this Symposium, particularly the paper by Dr. Skinner, in which I am especially interested. I believe that Dr. Skinner is going to help us a great deal with his emphasis upon what may be done to reduce the cancer mortality rate at the present time.

We all realize the great value of the work which Dr. Slye and many other research workers have accomplished. I think we are going to understand this work more in the future and I believe that great good will be accomplished by the added knowledge.

But we must not feel that it is going to take centuries to reduce the cancer mortality rate, because with our present knowledge of the subject we know that it can be reduced in the near future perhaps as much as 50 per cent, and that is immediately necessary.

There are so many things that enter into the great problem of reducing this mortality rate that it seems almost futile to attempt to discuss such a question in the period of a few minutes, but it is necessary, it seems, for radiologists to go home to-day with one thing in mind, at least—let us all try to do no harm to these patients!

You know, sometimes I wonder whether the physicians—taken as a class with the sum total of our accomplishments, taking us all, general practitioners and specialists—are really reducing the cancer mortality or whether we are elevating it.

That is a strange statement, but day after day patients come to my office, incurable because they have been mistreated by physicians, not only by general practitioners who may have enucleated a tumor of the parotid gland and disseminated the disease, but also by surgeons who, without any pre-operative irradiation, have performed a biopsy and disseminated the malignancy, and even by radiologists who have inadequately treated malignancy so that it is radioresistant and incurable.

It seems to me, then, that we can at least determine that we will go home with the idea that we will not do cancer patients harm. If we are inadequately equipped to handle them, let us turn them over to some one who is specializing in this complicated field.

I do not believe there is any branch of medicine more complicated or in which intense specialization is more needed, and this paper of Dr. Skinner has brought forcefully to our attention the fact that we should go out into the rural sections, because these patients are not coming to us. The farmer is busy with his crops and he will go a few miles to a clinic, but he will not travel many miles to a metropolis. We can all go out and teach our fellow-practitioners in the rural sections near us more about cancer—teach them to recognize it in its early stages, teach them to handle properly the simpler lesions and to refer such cases as are more complicated to some cancer specialist or cancer clinic where they can be properly handled. This is a definite remedy for a pressing need.

DR. SKINNER (closing): I feel that it is far more important to search for new methods of early diagnosis than for new cures —new methods of interesting physicians in early diagnosis.

Professional education upon facts that have advanced beyond consumption rates is already with us and this lag—this cultural lag—this educational lag—of the gap of time between facts and their application must be shortened.

THE ACTION OF ROENTGEN RAYS OR RADIUM ON INFLAMMATORY PROCESSES[1]

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WHENEVER treatment with roentgen rays or radium is mentioned, the idea that rises in the average mind is that the speaker or writer must refer to malignant tumors. Many physicians are not aware of the favorable influence of these agents on various forms of acute or chronic inflammation. And yet the therapeutic value of irradiation in inflammations has been so thoroughly substantiated and the testimony is so generally favorable that one wonders why the method is not used more than it is. Perhaps the very multiplicity of lesions for which radiotherapy has been claimed to be effective has led to a natural skepticism. Also, the multiplicity of explanations which have been advanced to account for the influence of roentgen rays or radium on inflammatory conditions has probably led many physicians to discredit the evidence or to ascribe it either to enthusiasm or to psychic factors. Indeed, without a satisfactory and convincing explanation, it would be difficult to believe that the same agent could be therapeutically effective against so many different forms of inflammation in different parts of the body. And yet the reason appears to be simple and rests on sound and abundant experimental evidence.

Others who have heard or read of the therapeutic possibilities of irradiation in inflammatory processes hesitate to make use of the method because they fear deleterious effects on the skin or gastro-intestinal disturbances such as are observed in connection with the treatment of malignant tumors. When treating neoplasms the aim is to deliver the largest dose compatible with the integrity of the surrounding tissues. When treating inflammatory lesions, on the contrary, only small or moderate doses are employed. Doses that might strain the tolerance of the skin are unnecessary and should be avoided as potentially dangerous. For acute inflammations especially, the doses required are so small that the skin or the gastro-intestinal tract cannot possibly be affected. Hence any fear on this score is unfounded.

The treatment of inflammatory processes with roentgen rays is far from new. Indeed, it goes back to 1902 and 1903. An interesting fact is that some of the earliest therapeutic trials were made in this country, but they did not receive any attention until the successful results had been repeatedly confirmed by others here and abroad. In connection with some varieties of inflammation the idea of treating them with roentgen rays arose from the chance observation of improvement following roentgenographic exposures for diagnostic purposes.

ACUTE INFLAMMATIONS

Many varieties of acute inflammation yield rapidly to a small dose of roentgen rays. By a small dose is meant a dose representing less than half of the tolerance dose of the skin; a dose as small as a fourth of the so-called erythema dose, or even less, is often sufficient, but this may vary somewhat according to the character and stage of the lesion in each case. A significant point is that the more acute the inflammation, the smaller the dose of rays required. With such small doses there can be no question of cutaneous or systemic reaction; therefore, weak and febrile patients can be treated without danger. In most cases a single

[1] Read before the meeting of the Baltimore City Medical Society, Baltimore, Maryland, March 5, 1937.

exposure is sufficient, but occasionally it may be advisable to repeat the treatment a few days later. This is particularly true when the initial dose has been exceptionally small or when the area treated has not been wide enough.

Pyogenic Infections.—Among the acute inflammatory conditions in which the therapeutic value of irradiation has been established are furuncle, carbuncle, abcess, cellulitis and phlegmon, onychia and paronychia, acute adenitis and erysipelas. Other forms of acute inflammation such as otitis and mastoiditis, pelvic infection, osteomyelitis, and gas-bacillus infection, also appear to be influenced favorably, but in connection with some of them the evidence is not yet absolutely conclusive.

In spite of the experimental observations of Schaefer (1), Motojima (2), and Lacassagne and Vinzent (3), and of the clinical testimony of Coyle (4), Dunham (5), Ross (6), Hodges (7), Heidenhain and Fried (8), Pordes (9), and many others, the method is not used as widely as it might be. Most of the authors mentioned agree that the majority of the patients derive prompt benefit. When irradiated early, during the stage of maximal leukocytic infiltration, many lesions do not suppurate; their evolution is arrested and they undergo spontaneous resolution. Therefore, the treatment is most effective when other methods of treatment are least effective; it is painless and does not interfere with the activities of the patient. Pain is often relieved in a few hours, but sometimes the relief of pain may be preceded by exacerbation for a brief period. Hot or other dressings are often unnecessary, or the period during which they must be applied is shortened. Treatment after suppuration has set in tends to hasten the suppurative process, the duration of which may thus be diminished more or less. Hence, the patients should be kept under close observation so that, if necessary, the surgeon may provide adequate drainage at the proper time. But acute pyogenic inflammations do not always respond so favorably; in a minor proportion of cases the inflammation yields little or not at all.

Pneumonia.—As early as 1905 and 1906, Musser and Edsall (10), and Edsall and Pemberton (11) were the first to observe and to report the strikingly favorable influence of a small dose of roentgen rays in four cases of delayed resolution of lobar pneumonia. Every other therapeutic measure having failed to improve the pulmonary condition of the patients, roentgen irradiation was tried as a last resort. Within twenty-four hours after exposure, resolution of the pneumonic exudate set in, proceeded rapidly, and the patients recovered. These observations were subsequently confirmed by Quimby and Quimby (12), Krost (13), and Torrey (14). In fact, the Quimbys were so impressed by the rapid influence of irradiation in ten cases that they were impelled to testify that "no pathologic process in the body responds quicker to an x-ray exposure than the non-resolution following pneumonia." Since then, Heidenhain and Fried (8), Holzknecht (15), Merritt and McPeak (16), and others have observed an equally favorable action of roentgen rays on post-operative pneumonia as well as on pneumonia unrelated to surgical intervention, in a large percentage of cases in which the treatment was employed. Naturally, the best results are to be obtained from early treatment. As pointed out by Musser and Edsall (10), irradiation cannot be expected to have much effect once the pneumonic inflammation has become organized or when the treatment is given shortly before impending death.

Parotitis.—Every surgeon is aware of the sinister character of that form of acute parotitis which arises as a complication of certain operations, especially on the large intestine, and of the high mortality associated with it. The first record of the favorable effect of irradiation on this disease appears to have been made by Heidenhain (17), who found that the inflammation reacted much as do other acute inflammatory processes. Rankin and Palmer (18) found that a moderate dose of

radium, applied soon after the onset, caused the inflammation to subside in most cases within from twenty-four to forty-eight hours. Moreover, suppuration usually did not occur, and the mortality was correspondingly reduced. Roentgen irradiation is just as effective but, in many cases, radium is preferable because the treatment can thus be given without disturbing the patient.

Erysipelas.—When erysipelas does not complicate diabetes or nephritis, roentgen irradiation is usually followed by prompt abatement of the fever and recession of the lesions. This is especially true when the patients are adults and when the treatment is given early. In children, for some unknown reason, the disease does not respond quite so well. In some cases, after an initial period of improvement, the inflammation may again become active, and additional treatment may be required to arrest the process. When this happens, it is usually because the initial treatment was confined too closely to the apparent limits of visible involvement. Too much stress cannot be laid on the importance of including in the field of irradiation a wide zone of apparently normal tissue around the lesion. A single dose, corresponding to 150 or 200 roentgens, of rays generated at 130 or 140 kilovolts, and filtered through 4 mm. of aluminium, is usually sufficient.

Favorable results may also be obtained by exposing the affected region to a strong, erythema or blistering, dose of ultraviolet rays. A possible disadvantage may be that, during the period of cutaneous reaction to treatment, it may be difficult to know what is disease and what represents reaction. Roentgen irradiation has no such disadvantage; the dose required does not cause reactive inflammation.

Other Acute Inflammations.—From time to time other acute inflammations are found to yield equally well to roentgen irradiation. Some years ago it was reported that in certain cases of acute mastoiditis, in which the mastoid region had been exposed to small doses of roentgen rays for diagnostic purposes, the inflammation had subsided and an operation had not been necessary. Similar reports have appeared since then, but some of these reports have been rather too casual to be convincing. I am not aware that the possible therapeutic advantage of irradiation in this condition has ever been given a serious and thorough test. This is unfortunate because, if acute mastoiditis should be found to yield as do so many other forms of inflammation, many patients might be saved some of the pain, mental stress, and cost of hospitalization associated with operations for mastoiditis. Moreover, this possibility could be tested without jeopardizing the interests of the patients in any way.

In 1936, Kelly and Dowell (19) reported that favorable results had been obtained in cases of gas-bacillus infection. According to them, the only patients who died were those whose affected extremity had been amputated. Inasmuch as the number of cases was not large and most of the patients had also been treated with serum, the evidence in favor of radiotherapy cannot be regarded as conclusive. But if Kelly and Dowell's experience should be repeated and confirmed by others, especially in cases in which patients were treated without benefit of surgery or serum, this would prove a great boon in a condition the gravity of which cannot be exaggerated.

CHRONIC INFLAMMATIONS

For years it has been known that many forms of chronic inflammation are favorably influenced by roentgen irradiation. Among these may be mentioned numerous varieties of chronic inflammation of the skin in which the therapeutic value of radiotherapy is conceded by experienced dermatologists. Other chronic inflammatory processes which may be mentioned as examples are tuberculous adenitis, peritonitis, keratitis, and iritis; actinomycosis and blastomycosis, trachoma in its early stages; and active, infectious arthritis. Two features which characterize the effect of irradiation are that the

dose of roentgen rays must be larger than the doses used for acute inflammations, and that treatment must be repeated at intervals for some time. By a larger dose is meant a dose varying between 50 and 80 per cent of the tolerance dose when given at one time or, in international units, between 300 and 500 roentgens, according to the conditions of irradiation. Rays generated at a potential between 120 and 140 kilovolts and filtered through 4 or 6 mm. of aluminium are usually adequate. Rays generated at higher potentials can be used with approximately equal effect, but this involves an unnecessary waste of energy. For skin diseases, unfiltered rays or rays filtered through 2 mm. of aluminium and generated at potentials of 80 or 100 kilovolts are generally preferable. The treatment of chronic inflammatory lesions with maximal (erythema, tolerance, or tumor) doses is bad practice and should be avoided as potentially dangerous. Since treatment must be repeated at intervals for varying periods, the use of maximal doses may lead to undesirable effects or, by superimposing a reactive inflammation, may cause the original inflammation to spread rather than to abate.

Tuberculous Processes.—Although considerable variation may be observed in different cases, the effect of irradiation is characteristically slow. In tuberculous adenitis the affected region must be irradiated every three or four weeks for from three to twelve months. When calcification is absent, the inflamed nodes gradually recede and may disappear completely or may remain as small fibrous granules. Unless abundant, caseous material may be absorbed or may be replaced by calcium. When suppuration occurs, drainage may be advisable, but sometimes the pus can be withdrawn through a needle of large bore, which should be introduced, not through the thinnest part of the fluctuant area, but to one side through more substantial tissue, so as to avoid the formation of a sinus. The extensive surgical procedures formerly in vogue are now seldom necessary. The resolution of tuberculous lesions appears to be hastened by supplementing periodic roentgen irradiation with daily exposure of the entire body to graduated doses of sunlight or to ultra-violet rays generated artificially. Ultra-violet irradiation confined to the affected region usually is a waste of time.

Much the same may be said of tuberculous peritonitis. An important consideration is that the entire abdominal cavity should be irradiated as uniformly as possible. This can best be done by dividing the anterior half of the abdomen from the level of the diaphragm to that of the pubic region into four fields, with the navel as the common center; the posterior half should be divided into four corresponding fields.

Physicians in general and many ophthalmologists are not aware that radiotherapy is an effective method of treating tuberculosis of the cornea or iris. The lesions recede more rapidly after exposure to roentgen rays than do similar lesions in other parts of the body. The dose of roentgen rays should never exceed three-fourths of a minimal erythema dose; a larger dose, especially in children, might lead to epithelial degeneration of the crystalline lens and to cataract.

Actinomycosis.—When actinomycosis affects the face, mouth, or other superficial structures, roentgen or radium irradiation, supplemented by the internal use of large doses of iodides and sometimes by simple surgical drainage of an abscess, are the most effective therapeutic measures, and a large proportion of patients can thus be permanently cured.

Not infrequently, actinomycotic inflammation arises in the intestine, especially the lower part of the small intestine, where it is often mistaken for simple or suppurative appendicitis. In many cases, one or more operations are performed, and the true character of the process is not recognized. This is unfortunate because, if the lesion is actinomycotic in character, exploratory maneuvers or any measure

beyond simple drainage of an abscess only serves to spread the infection. Thorough exposure of the entire abdomen (front and back) to about three-fourths of an erythema dose of roentgen rays may be followed by substantial improvement and sometimes by complete and permanent cure. Maximal improvement or cure requires that the treatment be repeated several times at intervals varying with the dose and the scheme of irradiation.

But when the infection has extended to the respiratory tract (bronchi, lungs, and pleura), more than slight and temporary improvement is not likely to be obtained with any method of treatment.

Trachoma.—Trachoma is characterized by conjunctival granulations composed largely of lymphocytes. Gradually these granulations are replaced by connective tissue, and the eyelids become sclerosed and distorted. As early as 1902 and 1903, Mayou (20), Stephenson and Walsh (21), and Cassidy and Rayne (22) made the discovery that, in some cases, the trachomatous granulations receded after exposure to roentgen rays, and that the patients were cured. Subsequently, Thielemann (23), Cochard (24), and Meldolesi and Sabbadini (25) confirmed the favorable influence of radiotherapy. Sometimes the lesions recurred later, but resumption of treatment caused them to retrogress and disappear; this probably meant that the initial treatment had not been continued long enough. The evidence furnished by the group of writers last mentioned indicates that the action of the rays is greatest during the early stages of the granular form of the disease and least during the late stages, when the granulations have been replaced by connective tissue.

Chronic Infectious Arthritis.—In many cases roentgen irradiation relieves pain, reduces swelling, and the functional disability diminishes. As might be expected, the degree of improvement varies considerably in different patients. The best results require repeated treatment and are obtained in cases in which the inflammation is active. Incidentally, a useful indication of active inflammation is tenderness. When the inflammatory deposits have become largely or completely organized, little improvement is to be expected. Of course, focal infection must not be neglected, irrespective of irradiation.

Recently, Berck and Harris (26) reported having treated with roentgen rays 30 patients with bronchiectasis, of whom 19 are said to have derived more or less pronounced improvement. Here again an opinion about the value of irradiation will have to await corroborative testimony. However, the care with which the cases appear to have been selected and the degree of improvement obtained in many of them make this report seem worthy of attention.

MODE OF ACTION

Acute Inflammations.—Numerous experiments have long since made it clear that most bacteria are not directly influenced to a perceptible degree by doses of roentgen rays or radium such as are commonly employed in treating human beings. To attribute the favorable effect of irradiation to a bactericidal action of the rays, therefore, would be to maintain an untenable hypothesis.

Anyone who has had an extended experience with radiotherapy for acute inflammations cannot have failed to be impressed by: (1) the prompt relief of pain and the rapid resolution of the lesions when treated early, as well as by the acceleration of suppuration in lesions treated later; (2) by the fact that acute inflammations of different kinds respond at about the same rate to a given dose when treated at a corresponding stage, and (3) by the circumstance that a small dose of rays is sufficient to produce this effect. Since irradiation acts in the same way and in the same time on so many forms of acute inflammation, it seems logical to conclude that the lesions themselves must have some common factor. This factor appears to be the radiosensitiveness of certain cells which are a more or less

prominent feature of the majority of acute inflammations.

Pyogenic infections in general are characterized by varying degrees of leukocytic infiltration. By accumulating leukocytes, chiefly lymphocytes, polymorphonuclear cells, and eosinophils, around one or more clusters of bacteria, the body attempts to localize the infection, to destroy the invading organisms, and to neutralize their toxic products. The leukocytic infiltration also appears to be Nature's method of intensifying the production of antibodies. An additional factor is hyperemia which facilitates the mobilization of leukocytes. Of some acute inflammations, especially those caused by streptococcic infection, local infiltration by leukocytes is not a prominent feature. Against infections of this kind the body apparently defends itself by a general reaction of the leukocytes in the circulating blood.

Experiments on a large number of animals of different species and observations on human beings of the effect of roentgen rays and radium on different kinds of cells and tissues have proved conclusively that each variety of cell has a specific range of sensitiveness to irradiation. Some are extremely sensitive, even to small doses, while others are not influenced by doses many times larger. Moreover, these experimental and clinical investigations have demonstrated that the most sensitive of all cells are the lymphocytes in the spleen, lymph nodes, lymph follicles, thymus gland, circulating blood, and bone marrow. The polymorphonuclear and eosinophilic leukocytes are also sensitive, but their susceptibility to irradiation is slightly less than that of the lymphocytes.

When the entire body of an animal is exposed to a moderate dose of roentgen rays or radium, the majority of the organs remain free from perceptible abnormalities, but the spleen, lymph nodes, and intestinal lymph follicles show a destruction of lymphocytes, the degree of which varies according to the dose of rays and the interval between irradiation and microscopic examination. As observed by Heineke (27), the disintegration of lymphocytes was characterized by disorganization and fragmentation of the nuclear chromatin of the cells and by scattering of the fragments of chromatin between the remaining intact cells and in the spaces of the reticular stroma, where the fragments gathered into clumps or balls. Then, the clumps or balls of degenerate chromatin were gradually taken up by some of the reticular cells, which assumed a phagocytic property and swelled as the amount of ingested chromatin débris increased. This was associated with a progressive reduction in volume of the affected lymphoid structures. Identical changes were observed in the lymphoid tissue of the vermiform appendix and in the bone marrow. The destruction of lymphocytes in the spleen and lymph nodes was often so great that most of the malpighian corpuscles or lymph follicles could be recognized only by the blood vessels and by the concentric arrangement of the stroma. A small percentage of lymphocytes appeared to resist the action of the rays. After a number of hours, the phagocytic reticular cells (macrophages) themselves began to disappear. The chromatin débris ingested by the phagocytes appeared to undergo intracellular digestion, because the number and size of the ingested fragments diminished steadily. Two or three days after irradiation, degenerative alteration of other cells, notably the polymorphonuclear leukocytes and eosinophils, also became perceptible, and many of these cells disappeared from the splenic pulp and bone marrow. From ten days to three weeks later, more or less regeneration of the lymphoid tissue became evident.

Since then, Heineke's (27) results have been confirmed by many investigators, including Krause and Ziegler (28), Fromme (29), Hall and Whipple (30), Warthin (31), Tsuzuki (32), and many others. Warthin's description of the effect of roentgen rays corroborated the observations of Heineke in every particular, ex-

cept that, by examining the tissue soon after irradiation, Warthin found unmistakable evidence of the disintegration of lymphocytes within fifteen minutes after exposure of the animals to the rays, and the cellular degeneration continued for several days. Similar effects have been obtained with radium. Other investigators have demonstrated that the lymphocytes in the circulating blood are equally sensitive to irradiation, and that the circulating polymorphonuclear and eosinophilic leukocytes are only slightly less sensitive than the lymphocytes.

The rate at which the varieties of leukocytes mentioned are destroyed by irradiation under experimental conditions corresponds closely to the rate at which acute inflammations subside after exposure to a suitable dose of roentgen rays or radium. The only other cells in the body which are affected at anything like the same rate are the mucus secreting epithelial cells in the salivary glands, in the bronchi, and in the intestine; but since these cells could not play any part in the majority of inflammatory processes, they may be excluded from consideration.

In circumscribed inflammations the significant rôle of lymphocytes, polymorphonuclear cells and eosinophils in the defense of the organism against infection and the sensitiveness of these cells to irradiation make it appear likely that, when an inflammatory process is irradiated, the rays act mainly by destroying a proportion of the leukocytes infiltrating the lesion or circulating in the blood vessels which supply the affected area. This view is corroborated by the rapidity with which the symptoms often abate and the physical signs disappear. Moreover, microscopic examination of irradiated inflammatory lesions has repeatedly shown destruction of leukocytes, especially lymphocytes, to be the outstanding feature observed. It seems logical to conclude, therefore, that destruction of leukocytes is the primary and direct effect of irradiation. As a result of the disintegration of infiltrating leukocytes the antibodies, ferments, and other protective substances which these cells contained are liberated in the surrounding tissue spaces, where they become mixed with the tissue fluids. It is also probable, as the experimental evidence indicates, that the next step is an increase in phagocytosis by reticular cells which become macrophages. No doubt other intimate, secondary, or indirect effects related to cell metabolism are produced, but the precise character and significance of these effects are not clear.

Since leukocytic infiltration is such an outstanding factor in the defense against infection, the natural question is why destruction of a large number of leukocytes infiltrating such lesions may not do more harm than good. The only answer is that, after small or moderate doses, no one has yet submitted any evidence of ill effects. The influence of irradiation always has been favorable or the rays have failed to alter the course of the inflammatory process. When I first attempted to ascertain the therapeutic value of irradiation for lesions of this character, this question was uppermost in my mind, and I carefully analyzed all the experimental and clinical facts. The first patients were treated with great caution. But after having treated hundreds of patients, I can testify that, although in some cases radiotherapy has not had a favorable effect, an unfavorable action has never been observed.

From the foregoing considerations, therefore, it seems not unreasonable to assume that irradiation, by destroying some of the infiltrating leukocytes, causes the protective substances in these cells to be liberated and to be made even more readily available for defensive purposes than when they were in the intact cells. This and the increase in phagocytosis which follows the disintegration of the cells represent the main effects of exposure to roentgen rays and radium and probably explain the usually favorable action of these agents. All the clinical circumstances indicate that inflammatory lesions respond to irradiation in proportion to the degree

of leukocytic infiltration. In favor of this view, held by Pordes and others, are the experimentally proved radiosensitiveness of lymphocytes, polymorphonuclear leukocytes and eosinophils, the fact that the rate of regression of acute inflammations corresponds to the rate at which these cells are known to be destroyed by irradiation, and that these cells are the only cells commonly found in inflammatory lesions that could be affected at such a rapid rate by small or moderate doses. Other circumstances pointing in the same direction are that radiotherapy is most beneficial during the infiltrative stage and less beneficial during the suppurative stage, and that, although the majority of lesions yields rapidly to treatment, some respond less rapidly or do not respond at all. Variation in the degree of leukocytic infiltration of different lesions of the same character or of similar lesions of different character is a well-known pathologic fact. Therefore, the degree of leukocytic infiltration must influence the action of the rays, because the rays can destroy leukocytes only in proportion to the number of these cells. This is undoubtedly related to and probably explains the fact that, while many inflammatory lesions are influenced favorably, some react much less or do not show any reaction.

When the inflammation is not confined to a small area but is extensive or diffuse rather than circumscribed, and when leukocytic infiltration is not a pronounced feature, as in erysipelas, the rays probably act in a somewhat different manner. Under these circumstances, the smaller number of infiltrating leukocytes should prevent the rays from having the same local effect, unless some compensatory mechanism enters into play. Evidence of such a mechanism in erysipelas has not yet been demonstrated, but that such a mechanism exists is indicated by the action of roentgen rays in other diseases. In bronchial asthma, for example, irradiation of the spleen or of other parts of the body remote from the bronchi and lungs is often followed by more or less striking relief from symptoms. What probably takes place is a destruction of leukocytes in the spleen and in the large mass of blood circulating through this organ. Then the cellular débris and the contents of the destroyed cells find their way into the general circulation, where they have been shown to produce a protein-like reaction. In inflammations that are not circumscribed and in which leukocytic infiltration is comparatively slight, the affected area is hyperemic and the vessels are more or less gorged with blood. Wide exposure of such an area to a small dose of rays undoubtedly causes many leukocytes to disintegrate, and the contents of the destroyed cells are liberated into the blood and throughout the tissue spaces. And the destruction of leukocytes is probably followed by changes similar to those described in connection with more limited inflammations. At least this would seem to be the most logical conclusion. Any other assumption would be inconsistent with the known facts and with the clinical behavior of this kind of inflammation.

Chronic Inflammations.—To understand the influence of irradiation on chronic inflammations it is necessary to bear in mind a few essential points. Depending on their character and on the etiologic factors which produce them, such lesions are characterized by varying degrees of leukocytic infiltration, connective tissue proliferation, and caseous or calcareous degeneration. Moreover, the clinical effect of irradiation is slow, and maximal improvement or cure requires repeated treatment at intervals. From what is known about the action of roentgen rays and radium on different varieties of cells and tissues, it seems most likely that these factors are closely related. Since they are products of cellular degeneration, cheese and chalk should not be influenced by irradiation, and this is precisely what is observed in practice. As we have already seen, the varieties of leukocytes which are such an important feature of inflammatory infiltration are exceptionally sensitive to roentgen rays or radium. Connective

tissue cells, on the contrary, are comparatively resistant to irradiation; they are even less sensitive than the epithelium of the skin. In this respect the difference between lymphocytes or polymorphonuclear leukocytes and connective tissue cells is tremendous. Analysis and correlation of these several factors would seem to furnish a satisfactory explanation of the effect of radiotherapy on chronic inflammatory processes. The greater the degree of leukocytic infiltration in proportion to connective tissue proliferation, the more marked and the more rapid is the influence of the treatment, and *vice versa*. If tuberculous lesions are taken as an example, it is well known that the effect of irradiation is greater during the infiltrative phase of the tubercles, when leukocytic infiltration is most pronounced than it is when the leukocytic infiltration has diminished and has passed into an advanced stage of caseous degeneration or of repair by connective tissue or by calcification. It is probable, therefore, that leukocytic infiltration, on the one hand, and connective tissue proliferation on the other, act in opposite directions, the former tending to increase the effect of irradiation and the latter tending to diminish or retard this effect. This conclusion is in complete harmony with the experimental evidence and with all the clinical observations which have been recorded.

In conclusion, one point should be strongly emphasized. When dealing with inflammations, the therapeutic radiologist must, as far as dosage is concerned, think in terms quite different from those that apply to malignant tumors. Even when treatment must be repeated many times, the dose of rays should never be sufficient to tax the tolerance of the tissues. Otherwise, the condition of some patients may be worse after treatment than before.

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ROENTGEN IRRADIATION OF THE HYPOPHYSIS[1]

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IN view of the increased interest in the pituitary body in relation to experimental and clinical endocrinology, and because of the frequent attempts to influence disease through irradiation of the adenomatous or non-adenomatous gland, it has seemed important to study the effects of irradiation of the normal pituitary body of the white rat.

During the past twenty years there have been numerous reports on the effects of irradiation of the hypophysis for various gynecological conditions, with varying results. Recently, irradiation of the pituitary has been extended to patients with diabetes mellitus and so-called essential hypertension, again with varying results. The question naturally arises, can the non-adenomatous pituitary gland be influenced with therapeutic doses of x-rays? A partial answer to this question could probably be obtained through animal experimentation. Apparently the first studies on the effects of pituitary irradiation in animals were made by Strauss (1) and Brunner (2), working independently in 1920. Strauss noted histologic changes in the pituitary body of the guinea pig after irradiation, but no changes in the other endocrine glands. Brunner irradiated the whole heads of young cats and puppies, and in addition to very slight histologic changes in the nervous tissue he found some histologic changes in the anterior pituitary. There was some suppression of growth after irradiation. Fraenkel and Geller (3), in 1921, irradiated the pituitary regions of young female rabbits. The irradiated animals grew less rapidly than the controls, and when killed they showed definite underdevelopment of the genital organs, including small uteri and small ovaries with infantile follicles. The pituitary bodies of the experimental animals were small, and many of the cells in the anterior and middle lobes had indistinct boundaries and contained irregular pyknotic nuclei. There was, however, no characteristic change in any particular cell. In 1922 Rahm (4) irradiated the hypophyseal regions of young rabbits. With smaller doses he noted stimulation of growth, and larger doses caused cessation of growth. There were no histologic studies.

Ghilarducci (5) also used young rabbits and claims to have found that many animals died after irradiation. At autopsy the internal organs were normal but there were skeletal changes with deformity, and complete destruction of the anterior pituitary glands, but apparently no changes in the ovaries or other endocrine glands.

Podljaschuk, in 1927 and 1928 (6-*a* and 6-*b*), using young and mature rabbits and dogs, and giving more than an erythema dose to the pituitary region, observed inconstantly, suppression of growth, and under-development of sex organs with histologic changes in the pituitary body. Del Buono (7), using slightly less than a skin dose in adult dogs, could demonstrate no structural changes in the hypophysis or other organs, six months to one year after irradiation. Mahnert (8) irradiated infantile white mice and observed inhibition of body growth and delayed estrus, associated with small uteri; also small ovaries with fewer ova, many in a degenerate condition. His method of irradiation is not given, so the effects may have been due to general irradiation of the whole body, in view of the small doses (100 r).

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Vischia (9), irradiating the hypophyseal regions of mature dogs, killed them after three months and found no histologic changes in the pancreas, suprarenals, or thyroid glands. No histologic studies of the hypophysis are given. Martinalli (10) observed no histologic changes in the pituitary of sexually mature rabbits after irradiation, but there was an increase in the interstitial tissue of the ovaries, and a decrease in the number of follicles. The uterine walls were hypertrophied. Some of the animals lost weight. Stockl (11) noted a decreased excretion of prolan A in the urine of young rabbits after irradiation. In 1932, Epifanio and Cola (12), irradiating young and adult rabbits, concluded that 25 per cent of an erythema dose accelerated growth, but that doses greater than an erythema caused suppression of growth. Some of the animals receiving the larger doses died, after losing weight and sex function, and having terminal convulsions. There were changes in the cells of the anterior lobe, the acidophiles being the most affected, and the testicles were decreased in size.

After irradiating young guinea pigs over the hypophyseal area, Migliavacca (13) observed atretic ovarian follicles and infantile uteri. In the older animals the changes were less marked. There were no microscopic studies of the pituitary body. Selle, Westra, and Johnson (14) studied the effect of pituitary irradiation on depancreatized diabetic dogs. Doses as high as 3,000 r were given. Histologically, the hypophyses showed congestion and degeneration and also some degenerative changes in the nervous tissue of the brain, but in spite of this there was no amelioration of the diabetes. Fehr (15), working in Lacassagne's laboratory, gave massive and fractional doses over the pituitary regions of sexually mature rabbits. The massive doses varied from 2,360 r to 2,645 r and the fractional doses varied from 3,300 r to 10,160 r. He calculated the dose reaching the pituitary to be about 80 per cent of the skin dose. After a single massive dose there was some loss of weight, but a gain occurred after fractionated treatment. The animals were killed four to six weeks after irradiation. There were no histologic changes in the hypophyses, and the other glands of internal secretion were normal except after massive irradiation, in which case the ovaries were small and had small follicles. The uteri were also small. These latter changes were not interpreted as results of pituitary irradiation. Fehr concluded that the pituitary of the rabbit is very radioresistant and cannot be influenced with ordinary doses of x-ray.

From the above summary of the literature concerning hypophyseal irradiation, one can conclude that the hypophyses of various laboratory animals are not very radiosensitive, although it is difficult to determine the doses used by most of the workers. The varying doses used, probably explains the lack of uniformity in the results obtained. There has also been no characteristic histologic picture in the pituitary body. In view of these inconclusive findings, we have studied the effects of pituitary irradiation on a large group of young female albino rats. No previous worker has used white rats, and since the endocrine system of these animals has been well studied and standardized histologically, they seem ideal for this purpose.

METHODS

Albino female rats, 30 to 40 days of age (usually litter mates), were used in each experiment. Under amytal anesthesia (controls included), the pituitary regions were exposed to filtered x-rays as follows: 180 kv., 25 ma., filter 0.5 mm. Cu and 1 mm. Al; 50 cm. distance, giving 52 r per minute. Except for an opening 1 cm. in diameter over the dorsum of the head directly over the hypophysis, the animals were shielded with lead. In a few animals the thyroid region was irradiated. Still others received the course of irradiations but the entire animal was protected with a lead shield. Control animals were given amytal at the time the experimental animals were irradiated. For several

TABLE I.—EFFECT OF IRRADIATION OF PITUITARY REGION OF RATS WITH 180 KV. FILTERED X-RAYS

Before Irrad.			After Irrad.		Remarks
No. of Rat	Wt. gms.	Dose in r	Day of Exp.	Wt. gms.	
12	50	Control	22	110	Killed on 23rd day
14		513 r on 1st, 7th, 14th, and 18th days	22	93	Killed on 23rd day
15	50	Control	22	114	Killed on 23rd day
16	51	Same as No. 14	18	105	Died on 19th day
17	48	Same as No. 14	22	98	Killed on 23rd day
18	48	Same as No. 14	18	101	Died on 19th day
19	46	Control	22	109	Killed on 23rd day
20	55	513 r on 1st, 7th, and 11th days	17	75	Killed on 20th day
22	57	Same as No. 20	17	89	Killed on 20th day
23	53	Control	17	101	Killed on 20th day
24	54	513 r on 1st, 7th, 11th, and 17th days	18	93	Killed around 19th day
25	54	Same as No. 24	17	77	Died on 18th day
26	55	Control	18	101	Killed around 19th day
31	56	1,040 r on 2nd and 8th days	13	46	Killed on 19th day
32	68	Control	41	148	Killed on 41st day
34	58	Control	13	103	Killed on 19th day
35	58	Same as No. 31	41	110	Killed on 41st day
37	67	Control	41	119	Killed on 41st day
40	58	1,040 r on 2nd and 8th days	41	98	Killed on 41st day
41	65	1,040 r on 3rd and 10th days	76	134	Died on 107th day
43	67	1,040 r on 2nd and 11th days	41	109	Died on 41st day
44	69	Control	76	187	Died on 76th day
47	63	Control	132	170	
48	63	925 r on 3rd and 8th days	13	80	Killed on 59th day
49	57	Control	13	82	Killed on 59th day
50	67	1,040 r on 3rd and 8th days	132	140	
53	60	1,040 r on 4th and 13th days	109	140	
54	60	Same as 53	27	95	Died on 32nd day
56	65	Same as 53	75	105	Died on 110th day
57	60	Control	109	165	
59	55	Control	58	175	(All killed on 58th day)
61	50	1,040 r on 5th, 13th, and 32nd days	58	120	
62	50	Hypophysectomy on 5th day	58	85	
66	40	Control	118	200	
70	40	Control	118	185	
71	45	1,040 r on 2nd and 7th days	64	110	Epilation not over pituitary. Killed on 64th day.
72	40	1,040 r on 2nd and 7th days	64	45	Died on 64th day
73	40	Control	64	115	Killed on 64th day
74	40	1,040 r on 2nd and 7th days	64	110	Epilation not over pituitary. Killed on 64th day.
76	40	Hypophysectomy on 7th day	64	70	Killed on 64th day
77	40	1,040 r on 2nd and 7th days	111	105	Died on 117th day
78	40	1,040 r on 2nd and 7th days	85	75	Died on 93rd day
79	40	1,040 r on 7th day	111	150	Received one dose of irradiation only
82	35	Control	111	155	
87	45	1,040 r on 1st and 4th days	27	40	Died on 28th day
88	40	1,040 r to thyroid on 1st and 4th days	28	85	Killed on 28th day
89	40	Control	28	95	Killed on 28th day
93	70	1,040 r to thyroid on 1st and 6th days	78	120	(All killed on 78th day)
95	65	1,040 r to pit. on 1st and 6th days	78	95	
96	70	Control	78	135	
98	50	1,040 r to thyroid on 5th and 11th days	56	125	
99	60	Same as 98	56	130	
101	50	1,040 r over animal covered with lead on 5th and 11th days	56	130	
102	60	Same as 101	56	130	
104	65	1,040 r on 1st day	3	62	Killed 3rd day after irrad.
106	55	1,040 r on 1st day	3	56	Killed 3rd day after irrad.
108	60	Control	3	65	Killed 3rd day after irrad.

weeks following irradiation, the animals were observed daily and frequently weighed. After a shorter or longer period of time, many of them were killed and autopsies were performed. The endocrine glands were examined grossly and microscopically.

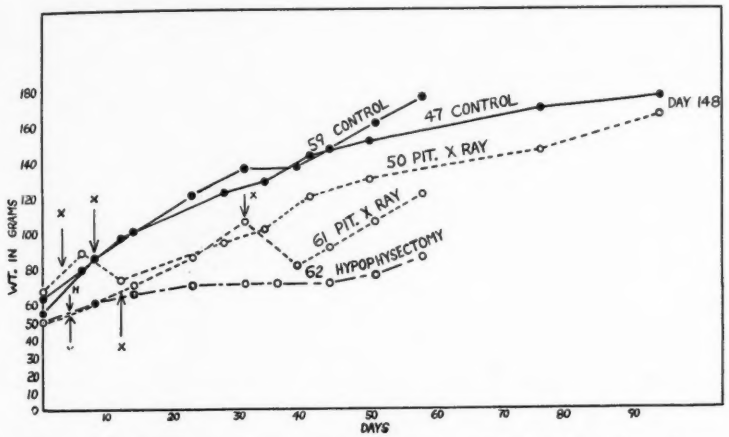

Fig. 1. Growth curves of two control rats, two irradiated and one hypophysectomized. (X = irradiation to pituitary. H = hypophysectomy.)

RESULTS

In Table I are tabulated the weights before and after irradiation with various doses. In the earlier experiments the animals were irradiated with 513 r at three or four different sittings, about five days apart. The inhibition of gain in weight was not striking, so that subsequently two doses of 1,040 r were given with a short interval between the two treatments. In all cases there was a subsequent temporary suppression or retardation in gain in weight.[2] Figure 1 shows the weight curves of a group of animals, one of which was hypophysectomized. The animals receiving irradiation gained much more slowly than the controls, the curves lying between those of the control and hypophysectomized animals. With these doses the retardation of gain in weight seemed to begin about one week after irradiation. As shown in Figure 1, animal No. 50, which received pituitary irradiation, weighed at the end of 148 days, nearly as much as the control No. 47. From these and other growth curves, it is difficult to determine the duration of the effect of irradiation on growth, but in most instances it did not last for more than ten days, the rate of growth subsequently showing an increase to parallel that of the controls. Often the irradiated animals developed the soft coats characteristic of the completely hypophysectomized animal. A few of the animals died sometime after irradiation, but this was not usual. The terminal coma was not relieved by subcutaneous glucose, so the deaths were presumably not due to hypoglycemia. A small group have been kept one year after treatment, and seem to be normal. No mating experiments for the purpose of determining fertility have been carried out.

A study of the individual and average weights of the adrenals, thyroids, and pituitaries of the irradiated and control animals (Table II) will show that the organs of the former were consistently smaller than those of the controls. As the averages include a number of animals which had shown, as judged by their body weights, a recovery from the effect of the

[2] In a few cases in which there was no definite suppression, the site of epilation over the rat's head indicated that the irradiation was off-center.

TABLE II

	Animal No.	Autopsied Day of Experiment	Ovarian Wgt. (mgm.)	Uterine Diam. (mm.)	Vagina	Stage of Cycle When Killed	Adrenal Wgt. (mgm.)	Pituitary Wgt. (mgm.)
C	12	23	60	2.5	Open	Dioestrum	42	8.5
X	14	23	42	3.0	Open	Proestrum	33	6.0
C	15	23	58	3.2	Open	Proestrum	43	8.2
X	17	23	38	3.8	Open	Oestrum	38	6.5
C	19	23	45	2.2	Open	Dioestrum	40	8.0
X	20	20	10	1.5	Closed	Dioestrum	28	5.0
X	22	20	16	1.5	Closed	Dioestrum	32	6.2
C	23	20	42	3.0	Open	Proestrum	42	8.5
X	24	19	28	2.0	Closed	Dioestrum	37	7.2
X	25	18	25	2.0	Open	Dioestrum	30	6.0
C	26	19	39	2.5	Open	Dioestrum	41	8.3
X	31	19	24	1.2	Closed	Dioestrum	27	5.1
C	32	41	42	3.5	Open	Oestrum	44	9.0
C	34	19	48	2.8	Open	Metoestrum	40	8.7
X	35	41	31	1.8	Open	Dioestrum	31	4.8
C	37	41	45	3.0	Open	Proestrum	45	9.3
X	40	41	37	2.8	Open	Proestrum	38	7.8
X	48	59	23	1.5	Open	Dioestrum	37	5.5
C	49	59	43	2.0	Open	Dioestrum	43	8.4
X	54	32	32	2.8	Open	Oestrum	36	6.5
C	59	52	63	2.8	Open	Metoestrum	59	9.0
X	61	58	29	2.0	Open	Dioestrum	29	4.5
H	62	58	19	1.7	Closed	Dioestrum	16	..
X	71	64	38	2.5	Open	Proestrum	39	6.5
X	72	64	15	1.2	Closed	Dioestrum	27	4.8
C	73	64	54	2.8	Open	Dioestrum	43	8.5
X	74	64	37	3.3	Open	Proestrum	38	7.0
H	76	64	11	1.2	Closed	Dioestrum	14	..
X	77	117	29	1.8	Open	Dioestrum	27	6.0
X	78	93	22	1.5	Open	Dioestrum	24	4.5
X	87	28	17	1.3	Closed	Dioestrum	23	4.0
XT	88	28	38	2.8	Open	Proestrum	39	7.3
C	89	28	42	3.0	Open	Proestrum	42	7.5
XT	93	78	45	2.5	Open	Dioestrum	44	10.5
X	95	78	27	2.0	Open	Dioestrum	31	4.5
C	96	78	43	3.2	Open	Proestrum	42	9.0
X	104	4	14	1.5	Closed	Dioestrum	26	4.8
X	106	4	15	1.2	Closed	Dioestrum	23	5.1
X	108	4	14	1.2	Closed	Dioestrum	27	5.0

	Averages		
	Ovaries (mgm.)	Adrenals (mgm.)	Pituitaries (mgm.)
X-rayed (19) animals	26	31.5	5.7
Controls (13) animals	48	43.5	8.5
Hyp.[2] (2) animals	15	15	..

[2] Although only two hypophysectomized animals are included in this series, data from over 20 young females hypophysectomized in a different experiment present confirmatory averages.

C = Control. X = X-ray to pituitary. XT = X-ray to thyroid. H = Hypophysectomy.

irradiation, the differences would be even more striking if only the animals under the more immediate influence of the irradiation had been included. A comparison of the organ weights for the irradiated animals with those of the hypophysectomized animals shows that the impairment induced by irradiation is not so marked as that following hypophysectomy. Indeed, the weights of the organs of the irradiated animals — and this is reflected in the histology of the organs — closely resembles that seen in cases of sub-total hypophysectomy.

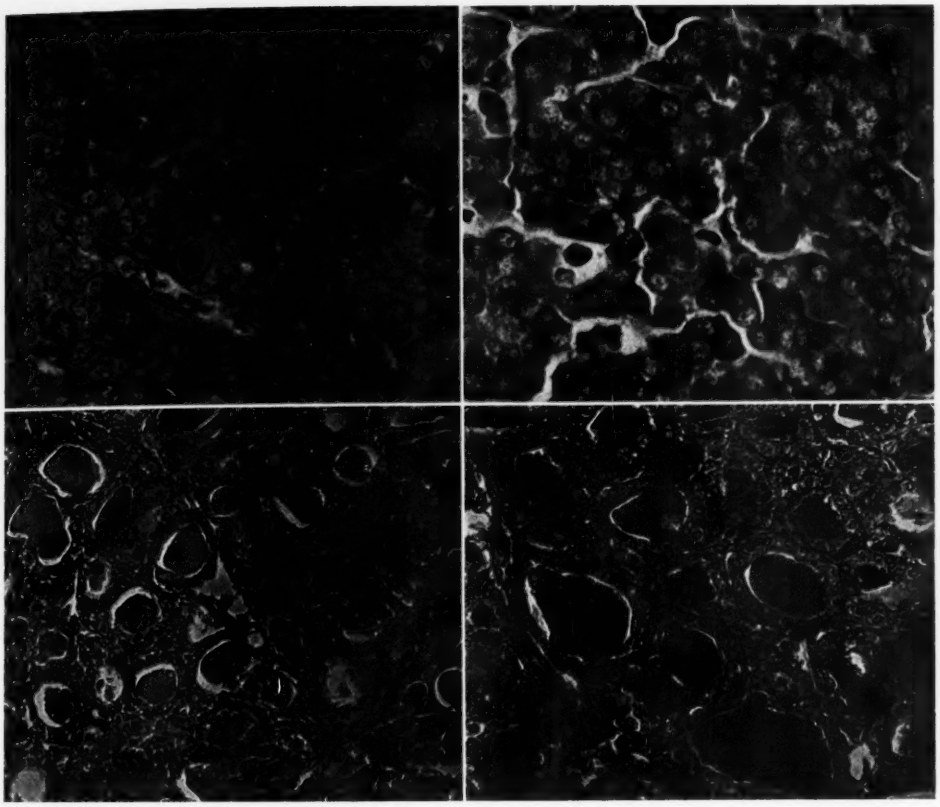

Fig. 2 (*upper left*). Hypophysis of Rat 20 (x-rayed). Sacrificed on twentieth day of experiment. Note absence of acidophiles and presence of numerous large basophiles. This selected area shows very few pyknotic nuclei (× 640).

Fig. 3 (*upper right*). Hypophysis of Rat 23, control for No. 20. Note presence of acidophiles. The basophiles, while fairly plentiful, are smaller and less numerous than for Rat 20 (× 640).

Fig. 4 (*lower left*). Thyroid of Rat 20. Note low epithelium (× 260).

Fig. 5 (*lower right*). Thyroid of Rat 23. Epithelium is normal in height (× 260).

All tissues have been fixed in Zenker-formol, embedded in paraffin, sectioned, and stained with either modified Mallory or Masson stains.

The typical picture observed in the hypophyses of the animals sacrificed from 18 to 22 days after irradiation is shown in Figure 2. The most striking difference between the experimental and control (Fig. 3) hypophyses is the scarcity of acidophiles in the former. Although no cell counts have been made in this study it is estimated that the granulated acidophiles are decreased from 50 to 75 per cent in the irradiated animals.

The basophiles, although less markedly affected than the acidophiles, show definite changes. In contrast to the acidophiles the number of basophiles is not reduced. Indeed, the pituitaries of the irradiated animals show a larger number of basophiles than are present in the hypophyses of the controls. Most of these basophiles are smaller than the usual granulated basophiles and the granules are distinctly clumped. Many nuclei in both basophiles and acidophiles are pyknotic.

The chromophobes have shown no significant change following irradiation except for the occurrence of pyknotic nuclei

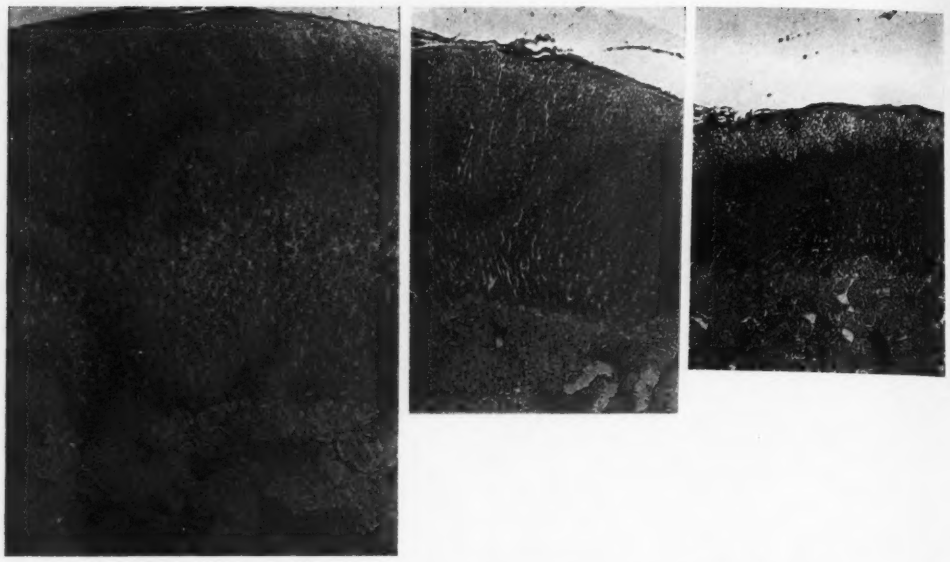

Fig. 6. Adrenals of three animals. The one on left is of Rat 59 (control); the middle section is of Rat 61 (pituitary x-rayed and animal sacrificed on fifty-eighth day); the section on right is of Rat 62 (hypophysectomy). Note decrease in cortical tissue in x-rayed and hypophysectomized animals (× 50).

and, of course, an increased number due to the decrease in acidophiles. It is quite possible that the chromophobes showing pyknotic nuclei were either basophiles or acidophiles at the time of irradiation and subsequently had undergone degranulation to a chromophobic condition.

The above description of the anterior pituitary of irradiated animals holds particularly for those sacrificed less than 27 days after irradiation. In animals sacrificed at later dates the hypophyses show, in most instances, definite evidence of recovery. The picture has varied from one similar to that already described to an almost normal condition.

There have been no significant changes in the posterior or intermediate lobes. In the latter, pyknotic nuclei are slightly more numerous than is observed in normal glands. The pituitaries of the animals sacrificed a few days after a single irradiation have shown little change.

The thyroids of the irradiated animals have been consistently smaller than normal. The follicles are smaller and the cells of the thyroid epithelium are low (compare Figs. 4 and 5). This condition is similar to that observed in the thyroids of hypophysectomized animals.

The adrenals of the irradiated animals were smaller than normal (Table II). The histologic picture shows this to be due to a decrease in cortical tissue, the medulla exhibiting little change. Although in this respect the effect of irradiation resembles that of hypophysectomy, close scrutiny of the cortical layers shows that the damage resulting from irradiation is much less severe than that following ablation of the pituitary (see Fig. 6).

The ovaries of irradiated animals have been consistently smaller than those of their controls (Table II). In the animals sacrificed less than 27 days after irradiation, corpora lutea were present in only one. Small follicles were present in these ovaries. All control animals of this group have shown at least two sets of corpora lutea (see Fig. 7). The ovaries of eight of the twelve animals continued for longer periods after irradiation showed corpora lutea. Two of these were rats, Nos. 71 and 74, in which the epilated area

indicated that the irradiation had been directed to one side of the hypophysis. The ovaries of these animals showed two sets of corpora lutea. In the ovaries of the other six, only single sets of corpora lutea were present.

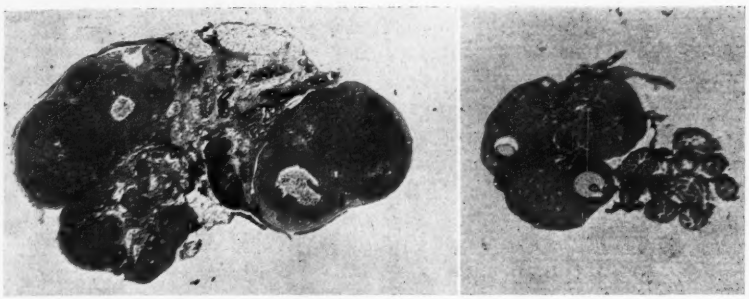

Fig. 7. On the left is ovary of Rat 23 (control). Several corpora lutea and large follicles are present. On right is ovary of Rat 22 (pituitary irradiated). Note small size and absence of corpora lutea (× 11).

The uteri and vaginæ of irradiated and control animals corresponded closely with the condition of the ovaries. In instances in which the ovaries were infantile the uteri were small and thread-like and the vaginal mucosæ low and castrate in type. In the other irradiated and in the control animals, the uteri and vaginæ showed conditions in harmony with the conditions of the ovaries from the same animals.

The vaginal smears of many of our animals were followed for a part or all of the post-irradiation period. The observations gathered by this procedure were in harmony with the condition of the ovaries and sex-accessories.

The possibility that the effects we have observed in our irradiated animals were due in part to a scatter of the x-rays to the thyroid glands seems to have been controlled by the study of animals whose thyroids only were irradiated. In these animals there was no significant disturbance in the growth rate, and the histologic condition of the hypophyses, adrenals, and ovaries was normal. The thyroids showed no effect of the irradiation. We are unable to make any statement concerning the immediate effect of irradiation on the histologic pictures of the rat thyroid since all of our animals were sacrificed some time after treatment.

DISCUSSION

Irradiation of the pituitary region, as carried out in our study, seems definitely to have depressed the activity of the anterior pituitary. This has been reflected in the suppression of growth, of ovarian activity, and in an atrophic condition of the thyroid and adrenal glands.

The preliminary studies made to determine the dosage of irradiation required to suppress hypophyseal activity show that the pituitary is relatively radioresistant. Furthermore, the irradiated gland is not permanently damaged as is shown by a gradual return of its structure and function to normal, or almost normal, conditions.

The pituitaries, ovaries, thyroids and adrenals of irradiated animals were definitely decreased in size. Inasmuch as these animals failed to grow normally we have considered the possibility of the lowered organ weights being simply expressions of the lower body weight. However, a comparison of the weights of such organs as the kidneys, liver, and heart expressed in terms of body weight with similarly expressed weights of pituitary, ovaries, thyroids, and adrenals has shown that the weights of the latter were less than would be expected on the basis of lower body weights only.

We are aware of the possibility that dam-

age to the hypothalamic region of the brain may have contributed to the effects we have observed. There is increasing evidence that this region of the brain may be related to anterior lobe activity. Its relation to the posterior lobe has been adequately demonstrated by Fisher, Ingram, and Ransom (16). We are unable to do more than call attention to the possibility that damage to the hypothalamus may have been a factor in our experimental results inasmuch as no examinations of the brains of our animals were made. The clinical picture we have observed is that of a deficiency of anterior pituitary hormones. The possibility that this deficiency may have been due in part to disturbed neurohypophyseal relations must await further study.

CONCLUSIONS

1. After irradiation of the pituitary regions of female albino rats 30 to 40 days old, there is a temporary decrease in the rate of growth.

2. Histologic examination of the pituitary glands consistently reveals characteristic changes which presumably account for the retardation of growth, the inhibition of ovarian activity, and the atrophic condition of the thyroid and adrenal glands.

3. From these observations it is fair to conclude that although the pituitary glands of young albino rats are relatively radioresistant, nevertheless they can be influenced by x-ray. The immediate period of suppression is followed by a gradual recovery of the pituitary and consequently, of the organs influenced by its hormones.

4. No definite clinical implications can be drawn but these experiments suggest that it is not unlikely that the non-adenomatous human hypophysis can be influenced with therapeutic doses of x-rays.

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THE ROENTGEN ANATOMY OF THE KNEE JOINT: AN EXPERIMENTAL ANALYSIS[1]

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INTRODUCTION

THROUGH their classical investigations concerning the analysis of bone form and bone transformation, Wolff and the earlier writers in the second half of the last century presented us with an understanding of bone architecture. Surprisingly enough this has never been followed by a systematic and detailed analysis of the skeleton as it presents itself in the living by means of the x-ray method. Here we see the three dimensions of bodily form, lacking depth, projected on the film in two planes only, thus making definition of the bony pattern an object of special analytical investigation. While study of the x-ray pattern of bones is based essentially on analysis of the bone architecture advanced by anatomists, roentgenology may, on the other hand, furnish information valuable to the anatomist. An impression of "the typical" (Francke) features of bone architecture, which cannot be secured by study of separate bone sections, will be produced by an x-ray image, which is the resultant of all the superimposed layers of bone in a given projection. Furthermore, radiographic study is the only method of analysis of normal and pathologic bone structure in the living, and in valuable anatomical specimens which should not be subjected to dissection.

Most authors who have concerned themselves with interpretation of the x-ray pattern of bones have used the method of comparative study of object and radiogram. This in itself proved insufficient to solve the more difficult problems of radiographic analysis. The study of Spalteholz specimens, *i.e.*, of bones made translucent by chemical treatment, while of distinct advantage in the analysis of radiograms, is of limited value for many of the problems of this paper. Besides, good results on larger and more complicated adult bones are hard to obtain and the specimens on the market are rather expensive. Stereography, although well fitted to give us an image comparable to the true object, is also unable to supply us with exact information as to the anatomical substrate of a certain line in the x-ray film. "Summation pictures cannot be united to a stereo effect since the real points pertaining to them are present neither on the picture nor in the object" (Francke). The object of the present report is the systematic analysis of the roentgenogram of the knee joint which requires detailed study on account of its complicated appearance and the clinical importance of the region.

METHODS OF STUDY

Four experimental methods of x-ray analysis were utilized. Roentgenograms were made before and after the following procedures:

(1) Chemical decalcification of the bony cortex or the spongious structure. Details of this method, which was used to determine the limitations of x-ray diagnosis of osteoporosis, are discussed in a previous paper (Lachmann and Whelan).

(2) Mechanical removal of cortex or spongious structure by means of emery wheels, files, drill-bits, and dental burrs (for removal of the spongious structure the bone was first sawed in frontal section).

(3) Serial sections of bones in frontal or sagittal planes perpendicular to the x-ray beam (see Figs. 1-*A* and 1-*B*). Simultaneously the bone was rebuilt, section by section, radiograms being taken at each stage.

[1] Aided by a grant from the Research Appropriation of the University of Oklahoma Medical School.

(4) Production of small defects at various levels within the cortex or trabecular structure, or within both, and examination by radiograms taken before and after the defects had been filled with an opaque medium. This method has great importance from the clinical point of view since it gives us an understanding of the x-ray visibility of destructive bone lesions (Chasin); in this connection it will be discussed in another report.

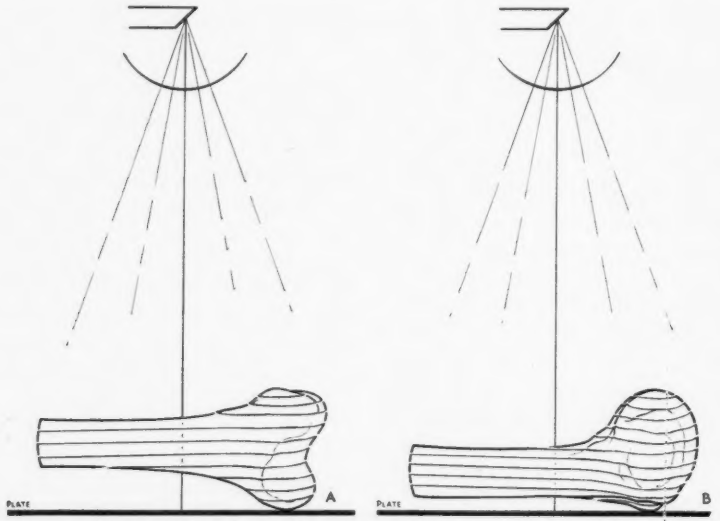


Fig. 1. X-ray analysis by serial sections. Bone is cut in sagittal (*A*) or frontal (*B*) planes perpendicular to the x-ray beam. Slices are removed, section by section, and roentgenograms are taken at each stage. Simultaneously the bone is rebuilt, section by section, and roentgenographed.

The four procedures outlined are all suitable for demonstrating the relative effects produced on the roentgenogram by the two components of bone, *viz.*, the cortex and the spongious layer. Procedure No. 3 is especially useful as a means of identifying a given line or point on the radiogram. Procedure No. 4, as already noted, is peculiarly adapted to show the limitations of the x-ray method.

X-RAY ANATOMY OF THE KNEE JOINT

A number of the more evident points in regard to the x-ray anatomy of the knee joint are discussed or illustrated in the appertaining text-books and atlases (Spalteholz, Cohn, Grashey, Brailsford). Valuable details are pointed out by Köhler ("The Borderlands of the Normal and Early Pathological in the Skiagram"). The bony development of the knee joint is considered in the atlas by Wilms and Sick, the work of Ruckensteiner, the extensive papers by Cohn, and by Ludloff. Filling of the knee joint with air or contrast medium is taken up by Hoffa, Boyd, Colp and Klingenstein, Bernstein and Arens, Simon, Hamilton and Farrington, the latter with extensive literature. The x-ray anatomy of the joint space and special projections for the demonstration of the intercondyloid fossa are discussed in the monograph by Hulten, the latter problem also by Kayser, and by Danelius and Miller, the former by Bauer and by Popovic and Doric. Joachimsthal treats of the structure, position, and anomalies of the patella.

One of the major problems pertaining to the x-ray anatomy of the knee joint which never has been sufficiently discussed is the relative part played, in producing the roentgenogram, by the two structural

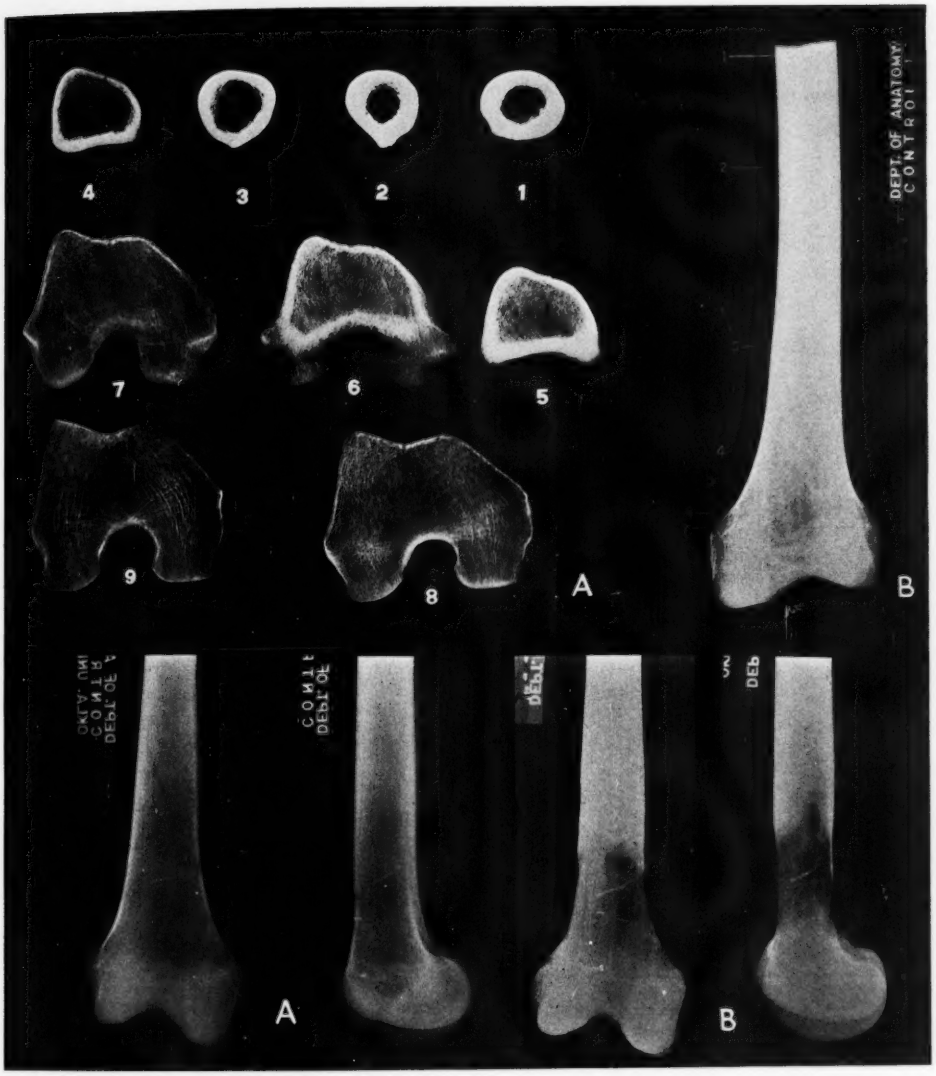


Fig. 2-*A* (*upper*). Roentgenograms of horizontal sections through shaft and distal end of femur. In the horizontal sections the lateral condyle is on the left, the medial on the right. Figures in *B* indicate levels of sections.

Fig. 3-*A* (*lower*). Roentgenogram of the distal end of a normal macerated femur.

Fig. 3-*B*. The cortex has been almost completely removed in the condylar and supracondylar portion of the same femur. The exposure has been adjusted to the greater translucency of the bone.

elements composing bone. Nevertheless this seems to us one of the fundamental questions in the analysis of a roentgenogram. The practical importance is evident. If we were able to show that one element, for instance, the cortex, is of greater significance than the other, we can immediately conceive of lesions of the spongious portion which may not be visible on the x-ray film and *vice versa*. Roentgenograms of cross-sections through the lower two-thirds of the femur at different levels (Figs. 2-*A* and 2-*B*) show the relative thickness of cortex and

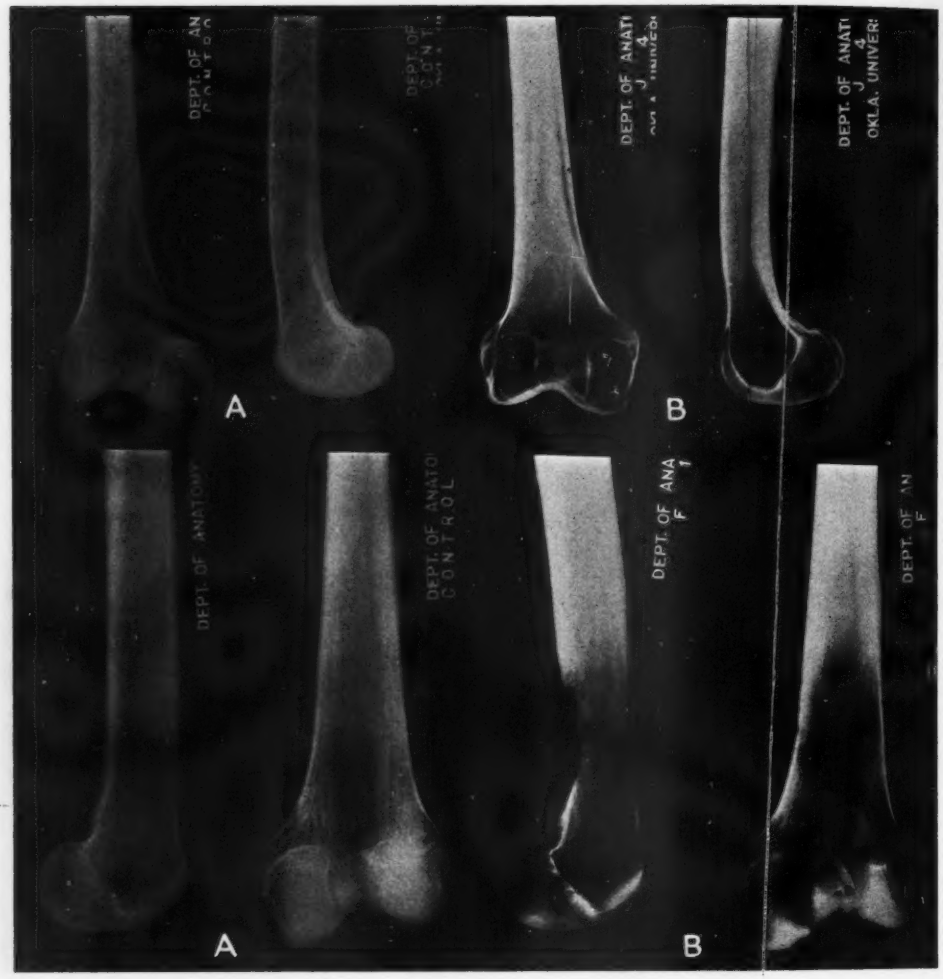


Fig. 4-*A* (*upper*). Roentgenogram of the distal end of a normal macerated femur.
Fig. 4-*B*. The same bone has been split and the spongious part almost completely removed. The exposure has been adjusted to the greater translucency of the bone.
Fig. 5-*A* (*lower*). Roentgenogram of the distal end of a normal macerated femur.
Fig. 5-*B*. The same bone with artificially produced, circumscribed defects, involving the cortex only.

spongious layer. It is to be noted that the diameter of the cortex gradually decreases toward the knee joint and the spongious layer gains in extent. From these facts we may come to the conclusion that the share of the two elements of bony structure in the roentgenogram changes at different levels. Further proof can be obtained from other experiments.[2] Figure 3-*A* proach the problem by the following consideration: If we decalcify two bones of the same type, one from the outside, the other from the inside—in this case protecting the outside by a coat of paraffin—and determine the amount of calcium removed by chemical analysis, the result would show up the relative significance of each part. In the event that we obtain positive results by destruction of the spongious part with less decalcification than by dissolving the cortex, we can say that the spongious layer is more important for the picture than the cortex and *vice versa*. This arrangement, while fitted for smaller bones like the carpals and tarsals, was not satisfactory for the long bones which are the object of our study in this paper.

[2] In a previously published group of experiments (Lachmann and Whelan, 1936) we attempted to ap-

shows the distal end of a normal macerated femur in front and profile views. Figure 3-*B* shows the same bone with the cortex almost completely removed in the condylar and supracondylar part. The exposure has been adjusted to the greater translucency of the bone. If the last illustration is compared with the control, it is surprising how few are the changes, although the cortex is almost completely absent in the lower part of the bone. We notice slight alterations in the contours. The details of the spongious pattern stand out more distinctly. Certain lines in the condylar area are absent.

If, on the other hand, the spongious layer is removed, we encounter a great difference. Figure 4-*A* shows a normal bone in both views. In Figure 4-*B* the bone has been split and the spongious part almost completely removed. The exposure has been adjusted to the greater translucency of the bone. The increased transradiancy varies in extent with the thickness of the cortex and is especially noticeable in the condylar and epicondylar area. While the contours of the bone are preserved, the structural pattern has almost completely disappeared. We notice also that certain lines visible within the bone on front view now stand out distinctly; they are, therefore, of cortical origin and represent the outlines of the condyles, seen on edge. Foramina nutritia, which on the control hardly could be differentiated from intertrabecular spaces, can now be made out in the supracondylar area on the front view. Attention will be drawn to a markedly translucent area on profile view, present above the condyles and which gradually fades toward the diaphyseal region of the bone. Its base at the level of the roof of the intercondyloid fossa is represented by a dense line running from above and posterior to below and anterior. It is called "Ludloff's spot," and will be discussed later.

By comparing Figures 3-*B* and 4-*B* we obtain an idea of the share each structure has in the production of the roentgenograph. If we imagine the cortex-free bone in Figure 3-*B* sunk into the spongious-free bone in Figure 4-*B*, we have a complete conception of the formation of the roentgenograph. We now understand that, in addition to the outline of the bone on the x-ray film, certain lines within the bone also are produced by cortical layers which are met on edge by the x-ray beam, while the structural pattern and the general opacity in the region discussed are due mainly to the spongious part. We view this trabecular arrangement as through a milky glass of different opacity, the intensity of which is determined by the thickness of the two layers of cortex parallel to the x-ray film.

From the facts discussed we come to several reservations which are the cause of a like number of diagnostic difficulties. Cortical, as well as spongious, structures are responsible for the absorption of x-rays and for the casting of the shadow on the film. Their respective shares depend on their relative thickness and will, therefore, vary in different regions. Thus increased translucency of bony substance, as we find it in atrophy, may be produced by disappearance of part of the cortical or spongious matter or by involvement of both. To determine decalcification as to the bony layers affected we must take into account the site of atrophy. Observation of the cortex where it is seen on edge will also help. Of importance, as well, is the fact that even in places where the cortex plays a relatively unimportant part, localized destruction of it, especially if not combined with general thinning of the cortex around the defect, will be recognized more easily than generalized removal of the cortex, due to the increased contrast between defect and surrounding areas. In Figure 5-*B* we have artificially produced a number of localized defects involving only the cortex. They are distinctly visible (Figure 5-*A* is the same bone untreated). The foramina nutritia within the cortex are examples of normal cortical deficiencies which may be mistaken for pathologic destruction.

Identification of certain lines within the bone has often produced controversial

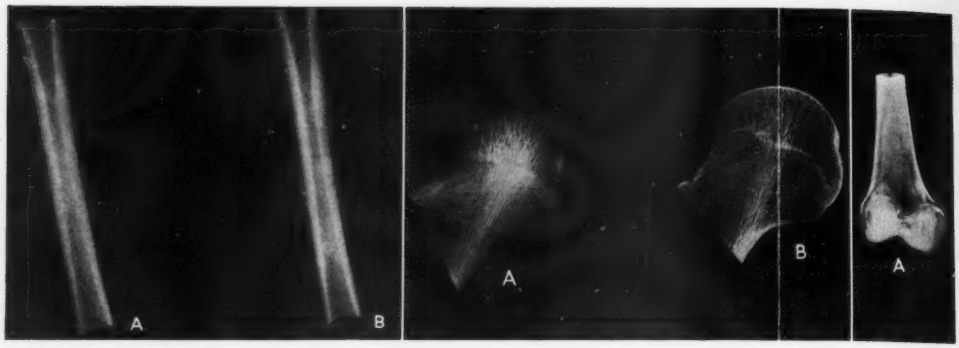


Fig. 6-*A* (*left*). Roentgenogram of the proximal two-thirds of a normal macerated femur shaft.
Fig. 6-*B*. The same bone with the spongious portion removed completely.
Fig. 7-*A* (*center*). Roentgenogram of the head and neck of a normal macerated femur.
Fig. 7-*B*. Roentgenogram of a thin section of the same bone.
Fig. 8-*A* (*right*). Roentgenogram of the distal end of a normal macerated femur. Medial condyle to the right, lateral to the left.

discussion. If they are visible within the silhouette on both views, we are inclined to localize them in the spongious layer, although they really may be part of the cortex seen on edge. This is especially the case in bony parts which have as complicated form as the distal end of the femur. While a certain oblique line in the cortex-free bone in Figure 3-*B* (which is probably due to old rickets), is certainly localized in the spongious layer, other lines farther down in the condylar area are of cortical origin as is shown in the spongious-free bone in Figure 4-*B*. The analysis of Ludloff's spot will illustrate this further.

Each area has to be judged according to its own merits. Figure 6-*A* shows the proximal two-thirds of the normal femur shaft below the intertrochanteric region. Figure 6-*B* is the same bone with the spongious portion removed completely. In the relation of thick cortex to small amount of spongious layer we see the reason for the almost identical appearance of the two roentgenograms (compare with cross-sections 1, 2, and 3 of Figure 2). A destructive lesion involving only the spongious layer in this area would not show up at all on the x-ray film.

Since the importance of the spongious structure has been emphasized sufficiently, it is also necessary to keep in mind that the spongiosal pattern which we see on the roentgenogram does not correspond to individual layers of bone trabeculæ, but that it represents a superposition of many strata of spongious bone which lie in the plane of the x-ray beam. The roentgenographic image of the bony meshwork is produced by a summation effect (Francke). By a very ingenious arrangement Francke has shown that two femora, which are superimposed on an x-ray film, may cast exactly the same shadow as one, in the same way as an x-ray film of a thin section of bone may be almost identical with that of the whole bone (taken, of course, under different conditions of exposure). Figures 7-*A* and 7-*B*, in which *A* is the roentgenogram of the head and neck of a complete femur, and *B* of a thin section of the same bone, illustrate this. Thus it becomes clear that destructive foci within the spongious bone must attain a certain size in order to become visible on the roentgenogram. Many other factors are also involved, for instance, the relative and absolute thickness of the two layers composing bone, the density of the structures surrounding the defect, and the quality of the x-ray beam. From the facts presented we arrive at a clearer understanding of the limitations of the x-ray method.

A detailed analysis of the roentgeno-

gram of the knee joint requires a separate study of the standard projections. Many of the important facts can be gained by stereoradiography and by comparison of object and x-ray film, while the semi-translucent Spalteholz specimens are especially helpful. These facts are enumerated in the literature quoted above. Other important points of practical interest become evident only by use of serial sections, a method which has been described above. They will now be discussed.[3]

DISTAL END OF FEMUR (FRONT VIEW)

Direction of the x-ray beam: postero-anterior.

A roentgenogram of a normal femur (Fig. 8-*A*) in this projection shows the lateral condyle to be less translucent than the medial, a fact explained by the arrangement of the trabeculæ as shown on cross-sections of the femur (Fig. 2, sections 6–9). It is not so much the greater density, which has been pointed out by Krause and which has been given as the reason in the literature (Hulten), although this may also play a part, but rather the direction of the trabeculæ in relation to the x-ray beam. Only in the case of the lateral condyle do they run almost in the same plane as the x-rays. The importance of this normal difference in translucency of the condyles can be gathered from the following quotation from Köhler:

"Tuberculosis has frequently its site in one of the femoral condyles. The first changes occur in the bone, but do not catch the eye immediately in the roentgen picture; they occur, not in the form of foci, but more in the form of a diffuse translucency of the affected condyle easily recognizable as such."

Thus the normally greater transradiancy of the medial condyle may be mistaken for tuberculosis. Other things being equal, atrophy will be more marked also on the medial side. Hulten and Schinz report that the difference in density between the lateral and medial condyles is more pronounced in genu valgum.

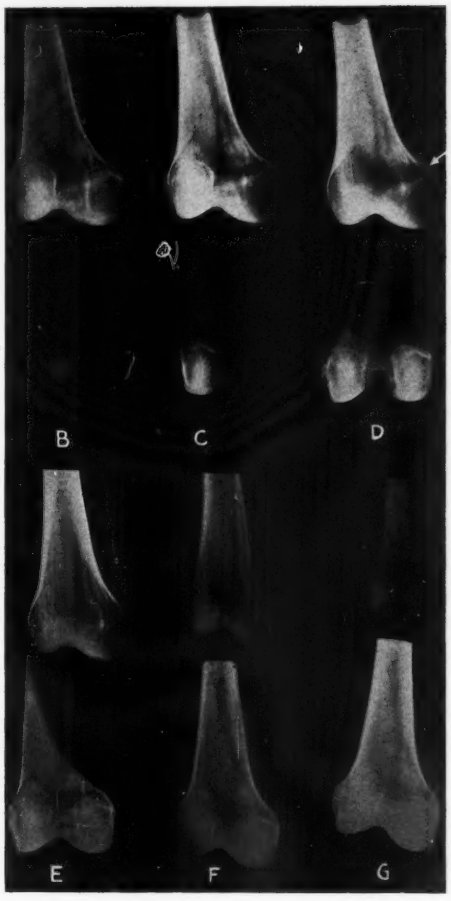
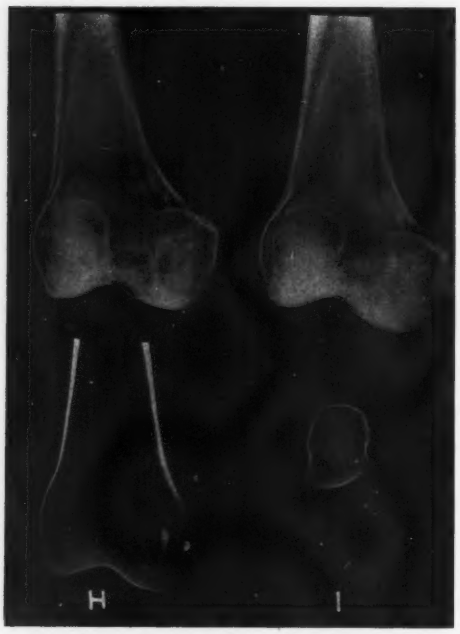


Fig. 8-*B* to *D* (*upper*). Roentgenograms of the same femur as in the control Figure 8-*A*. The bone has been cut in 11 serial sections in frontal plane (compare Fig. 1-*B*). In each consecutive roentgenogram one or more sections have been removed. The removed parts are always shown underneath. In Figure 8-*B* a fragment of 5 mm. thickness is taken from the posterior surface of the medial condyle; in *C* the whole medial condyle is removed; in *D* both condyles with part of the bone around the intercondyloid fossa. Medial condyle to the right, lateral to the left. Arrow at the adductor tubercle on *D*.

Fig. 8-*E* to *G* (*lower*). See caption for Figures 8-*B* to *D*. In *E* the bone has been divided into a larger anterior and a smaller posterior portion, which includes the condyles. *F* shows the bone divided in a smaller anterior and a larger posterior portion. In *G* only a thin part of the anterior cortex with some spongious structure is left.

Figures 8-*B* to 8-*G* show roentgenogram

[3] A structural analysis of the femur on a mechanical and mathematical basis, for which roentgenograms are very helpful, is not within the scope of this paper. In this respect reference is made to the investigations by Wolff, Gallios and Bosquette, Gebhardt, and Koch.



Figs. 8-*H* and 8-*I*. Roentgenograms of the same femur as in the control Figure 8-*A*. In *H*, a fragment from inside the bone has been taken out, containing mostly trabecular structure; in *I*, a section from inside the lateral condyle. Medial condyle to the right, lateral to the left.

F of the same femur as the control film, 8-*A*. The bone has been cut in 11 serial sections (5–8 mm. thick) in frontal plane. In each consecutive roentgenogram one additional section has been removed.[4] The removed parts are always shown underneath. In Figure 8-*B*, a fragment of 5 mm. thickness is taken from the posterior surface of the medial condyle; in *C*, the whole medial condyle is removed; in *D*, both condyles with part of the bone around the intercondyloid fossa. In *E* the bone has been divided into a larger anterior and a smaller posterior portion, which includes the condyles, *F* shows the bone divided in smaller anterior and a larger posterior portion, and in *G* only a thin part of the anterior cortex with some spongious structure is left.

Thus a detailed analysis of the x-ray pattern of the femur is made possible and every line on the film can be localized as to its anatomical substrate. Figure 8-*B* demonstrates the share of a thin cortico-spongious layer in the production of the general opacity of the picture; in *C* we observe that the distinct lines in the roentgenogram of the condylar area are produced by the contour of the condyles seen on edge. Figures *C* and *D* also prove that the x-ray pattern is the expression of a summation effect of different layers of spongious structure, since the arrangement of the trabeculæ is undisturbed, although a considerable part of trabecular structure has been removed. In Figure *E* an area of condensation within the spongious structure, a so-called "compact island," which is hardly visible on the control, now appears very distinctly. Thus we may assume that these compact islands are more frequent than we would expect from the study of roentgenograms. We found them in our sections in several cases.

An irregularity on the lateral side of the lateral condyle is easily discerned as corresponding to the groove for the tendon of the popliteus muscle, as can be recognized from the fragments in Figures 8-*D* and 8-*E* below.[5] It should not be mistaken for an arthritic change. The same holds true for the adductor tubercle which is visible above the medial condyle (arrow on Figure 8-*D*). Other irregularities in the contours of the condyles may be due to the insertion of the collateral ligaments.

In Figure 8-*G* with only a very thin layer of mostly cortical bone remaining, we see the numerous foramina nutritia as small defects which now can also be identified on the control, although much more indistinct.

As was to be expected from what had been said before, this thin layer of bone has no influence on the pattern. The picture in Figure 8-*G*, below, is almost identical with the control. The influence of single slices of bone in the roentgenogram becomes

[4] A number of roentgenograms of intervening sections are not shown here.

[5] In reality there are several grooves for the tendon in the positions of extreme flexion, moderate flexion, and extension, as H. Virchow has shown (quoted from Krause).

clearest if we remove just one layer of bone and roentgenograph the rest. While Figure 8-*G* illustrates the influence of a thin cortical slice which lies parallel to the x-ray film, Figure 8-*H* illustrates that of a fragment from inside the bone which contains only trabecular structure (except for a thin shell of cortex which is in line with other parts of the cortex seen on edge). No distinct change is produced if we disregard the disappearance of the compact island. In Figure 8-*I* a bony fragment of about 5 mm. thickness, consisting of spongious structure and a thin cortical layer which runs in different directions to the x-ray beam, has been removed from inside the lateral condyle. We see no change in the translucency of the bone. The lateral condyle still is more opaque than the medial. Where the cortex of the fragment participated in the formation of the condylar contour we see disappearance of those lines. In other areas where the cortex was arranged in a plane oblique to the x-ray beam, as in the upper medial corner of the lateral condyle, we notice a distinct defect.

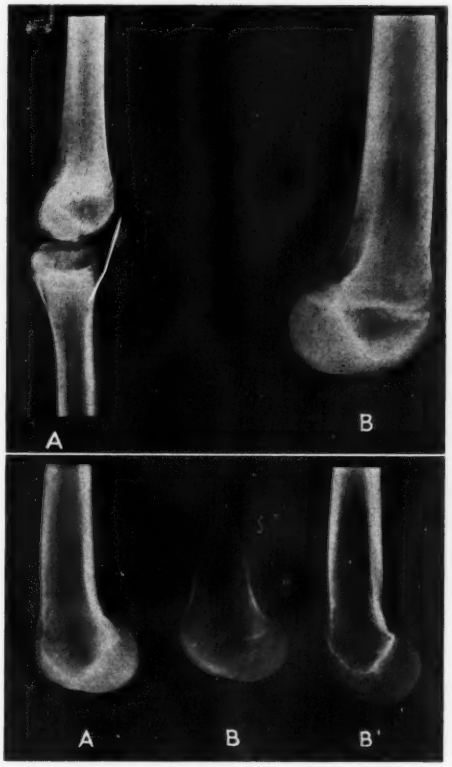


Fig. 9-*A* (*upper*). Lateral view of a knee joint; patient aged 5.

Fig. 9-*B*. Lateral view of a femur; patient aged 16. Both roentgenograms show Ludloff's spot.

Fig. 10 (*lower*). Analysis of Ludloff's spot by section method.

Fig. 10-*A*. Lateral view of the distal end of a normal macerated femur.

Fig. 10-*B*. Slices containing the medial condyle and the intercondylar area have been removed. *B'* shows the removed fragments. Distal contour of Ludloff's spot has disappeared in *B*.

DISTAL END OF FEMUR (PROFILE VIEW)

Direction of the x-ray beam: medio/-lateral.

The analysis of the profile view of the femur undertaken again by serial sections in planes vertical to the x-ray beam leads us to a discussion of Ludloff's spot. This is a translucent area which appears on lateral view of the normal femur in the anterior portion of the condylar region (Figs. 9-*A*, 9-*B*, and 10-*A*). It is approximately triangular in children, while in adults its upper contour is indefinite. Here it gradually passes over into the more translucent central region of the diaphysis. Ludloff, after whom this area is named, was the first to point out that it is absolutely normal and should not be mistaken for any destructive focus, for instance, tuberculosis (Ludloff, Köhler). Referring to Ludloff's paper, Köhler gives the following definition of this area:

"This epiphyseal spot is quite a normal appearance; it shows in the interior a fine network of bony trabeculæ and is not sharply delimited by a single line, but by the trabeculæ running to its edge being denser. It is said to correspond to the place in both condyles where numerous nutrient vessels enter the condyle and where the reflexion of the synovialis is situated. It appears most prominently about the sixteenth year. Thereafter it passes without any definite dividing line into the transparency of the interior of the diaphysis. Its distal anterior and posterior contour correspond to the corticalis of the femur between the two condyles."

Grashey describes the translucent epiphyseal spot as framed in its distal portion by a plug-shaped zone of denser osseous

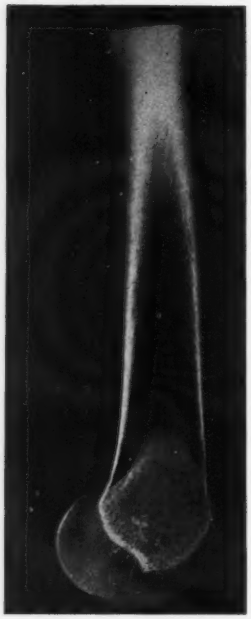


Fig. 11. Roentgenogram of three sagittal sections of macerated femur, put together, two adjacent ones representing two peripheral sections from medial condyle and a third of about 7 mm. thickness corresponding to the center of the intracondyloid area. Slices are arranged according to their natural position in the complete bone. Distal contour of Ludloff's spot is visible.

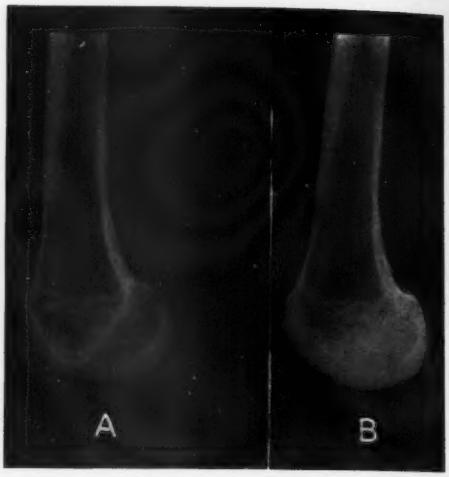


Fig. 12-*A*. Lateral view of a normal macerated femur, showing Ludloff's spot.

Fig. 12-*B*. A narrow cortical zone of about 1 cm. in width has been filed away all around the distal end of the bone. The distal contour of Ludloff's spot has almost completely disappeared.

tissue. "This plug corresponds, partly at least, to the bony bridge between the two condyles."

In analyzing the area in question we have to distinguish between its dense contours and its translucent interior. As to the contours the definition by Köhler is somewhat inconsistent. On one hand we learn that the spot is not sharply delimited by a single line but by the trabeculæ on its edge being denser, on the other that its distal anterior and posterior contours, which are the only contours we can make out in the adult, correspond to the corticalis of the femur between the two condyles.

We used a number of methods to solve this problem. From Figures 9-*A* and 9-*B* it is clear that the proximal boundary of the area in children is the epiphyseal line and correspondingly in an adult bone (Fig. 10-*A*) we see the old epiphyseal scar going through the region as a faint, indistinct line. The analysis with our section method shows that the distal contour of the spot disappears when the slices containing the intracondylar cortex are removed. Figure 10-*B* demonstrates this (*B'* shows the removed fragments). This investigation was supplemented by the following arrangement. Only three slices of another bone were roentgenographed, two adjacent ones representing the two peripheral sections from the medial condyle and a third of about 7 mm. thickness which corresponds to the center of the intracondylar area. The slices were arranged according to their natural position in the complete bone. Figure 11 shows the roentgenogram. We see the lines corresponding to the distal contour of Ludloff's spot produced by a cortical zone of not more than 7 mm. in thickness. Thus we realize that it is not the whole intracondylar cortex which bounds Ludloff's area, but just that central part which lies exactly in the direction of the x-ray beam, while the adjacent sloping portions play only a small part in producing this distinct demarcation.

To obtain the final proof, we filed away a small cortical zone about one centimeter in width all around the distal end of another femur in the intracondylar plane. The result is shown in Figure 12-*B*; 12-*A* depicts the same bone untreated. We see

that the distal contour of Ludloff's spot has almost completely disappeared. The epiphyseal scar is visible as an indistinct line interrupting the translucency.

Ludloff stresses especially the fact that the increased transparency of the interior of this region is produced by superimposed areas of greater sponginess in both condyles and in the intracondylar field. While this may be true to a certain extent, the roentgenograms of our spongious-free bone (Fig. 4-*B*) demonstrate beyond doubt that it is not the arrangement of the trabeculæ which is the cause of the increased transparence, but the change in thickness of the cortex. In judging the translucency

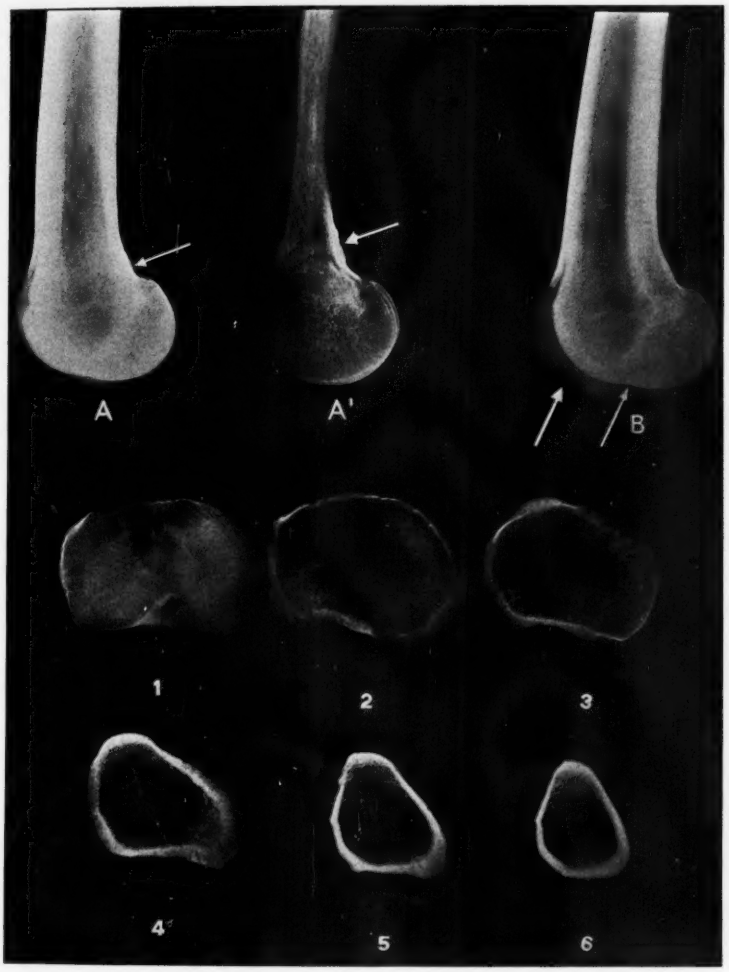


Fig. 13 (*upper*). Profile view of the lateral (*A*) and medial portion (*A'*) of the distal end of a macerated femur, showing the origins of the lateral and medial head of the gastrocnemius muscle as distinct protrusions on both fragments in the region of the planum popliteum (arrows on *A* and *A'*).

Fig. 13-*B*. Depicts the limiting grooves, mentioned in the text, on both condyles (arrows on 13-*B*).

Fig. 14 (*lower*). Roentgenograms of horizontal sections through upper epiphysis and proximal part of shaft of tibia.

of an area we do not use any absolute measurements, but compare it with the relative density of the surroundings. In our case we compare it with the density of the condylar region, which is brought about by four layers of cortex, and of the distal end of the shaft, the cortex of which gradually increases in thickness toward the femoral head (compare horizontal sections Fig. 2). Finally we see that the lateral view of the cortex-free bone (Fig. 3-*B*) shows no trace of Ludloff's spot.

Summarizing our findings in this respect we state that the distal anterior and posterior contours of Ludloff's spot are formed by a narrow zone of intracondylar cortex and that the increased transparency of the region is produced by the change in the diameter of the cortex which is especially thin in the area in question.

Some other points in the analysis of the profile view of the femur which are of practical importance will be discussed. Often we notice on the posterior contour of the femur, in the area of the planum popliteum, a pointed process which may be mistaken easily for an arthritic spur. It is normal, although it may be enlarged in arthritis (Köhler), and corresponds not so much to the insertion of the adductor magnus (Grashey), which is farther in front, but to the origin of the medial or lateral head of the gastrocnemius or of the plantaris muscle, if lateral. That it may depict a roughness of the planum medially or laterally is proven by Figures 13-*A* and *A'*, where the process is visible on the sections comprising the lateral (*A*) as well as the medial (*A'*) part of the bone (arrow on *A* and *A'*).

Attention may be directed also to a misleading irregularity of the inferior articular surface of the condyles where it passes into the anterior articular plane. It corresponds to a limiting groove on the inferior surface of the condyles which is produced by the anterior border of the tibia at the site where it reaches the femur in the position of extreme extension. According to Mikulicz and Krause it is more pronounced on the medial condyle. Figure 13-*B* which projects the femur in an oblique position after part of the medial condyle has been removed, shows the limiting grooves on both condyles, much more distinct on the lower and medial than on the lateral (marked by arrows). As Hulten points out, these grooves may appear also on anteroposterior view and may then lead to the wrong diagnosis of an arthritic change. Like all normal anatomical irregularities these grooves become more marked with increasing age (Hulten).

TIBIA (PROXIMAL END)

A study of cross-sections through the proximal end of the tibia furnishes us with an understanding of the share of the cortical and spongious structures in the production of the roentgenogram. In Figure 14, which depicts horizontal sections through the condylar region and the proximal part of the shaft, we notice the same relations in the amount of cortical and cancellous tissue as we found in the distal end of the femur. The closer to the joint, the thinner becomes the cortex and the larger the share of the spongious tissue (Fig. 14, sections 1 and 2), while in sections 3 to 6 through the shaft at the level of the tuberositas tibiæ the cortex has increased in diameter and the trabeculæ are arranged in loose tracts according to the lines of internal stress. We may conclude that here also—analogous to the femur—the importance of the two structures changes with the level of the bone. Therefore that which has been said in the first part of this paper in this respect regarding the femur, holds true also for the tibia.

PROXIMAL END OF TIBIA (FRONT VIEW)

Direction of the x-ray beam: anteroposterior.

In Figure 14, sections 3–6, we observe that spaces are left between the trabecular columns where we find no, or very few bony laminæ. This gives us an explanation for the presence in the roentgenogram of areas "poor in lime about the size of peas which one sometimes meets directly underneath the intercondyloid tubercles"

(Köhler). See the normal control, Figure 15-*A*. Foramina nutritia, which are numerous in this region and which are

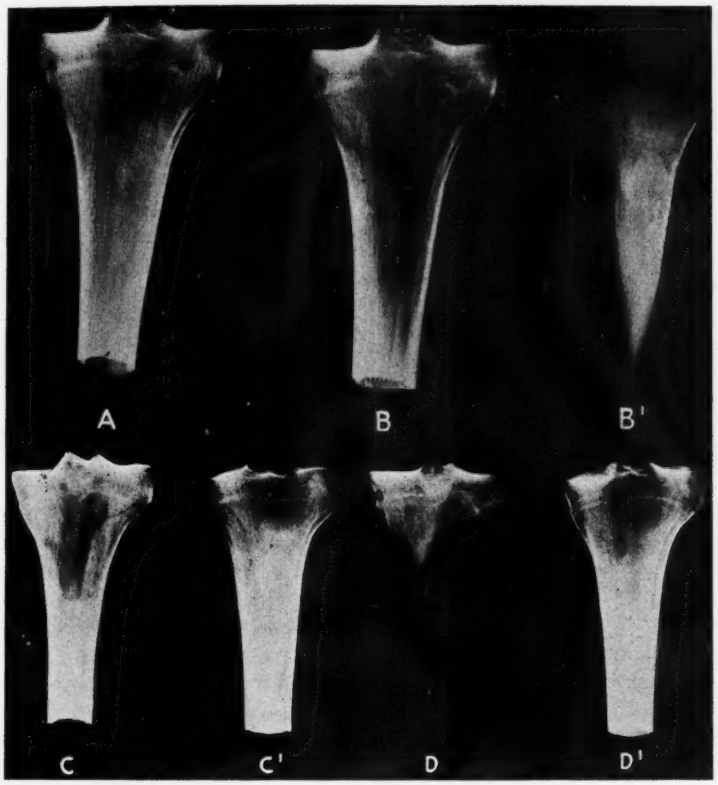


Fig. 15 (*upper*). Serial sections through proximal end of tibia. Medial condyle to the left, lateral to the right.

Fig. 15-*A* is the normal control. In Figure 15-*B* a thin section from the anterior surface of the bone has been removed. *B'* shows the removed portion.

Fig. 15-*C* (*lower*) shows the same bone as in Figure 15-*A* divided into a posterior (*C*) and an anterior half (*C'*). In Figure 15-*D* only one section from the posterior surface of the bone has been left; Figure 15-*D'* depicts the removed portions.

visible on our first frontal section (Fig. 15-*B'*), may add to the spotted translucency. On horizontal sections (Fig. 14, 3–6), we notice a pronounced cortical protrusion corresponding to the tuberositas tibiæ. On anteroposterior view this appears as an ill-defined density of the shaft below the epiphysis, lateral to the middle line (Fig. 15-*B'*). The roentgenogram in Figure 15-*C* still resembles the control very much, although more than half of the thickness of the bone has been removed. We notice disappearance of the upper curved contour of the articular surface of the medial condyle. This curved line, therefore, corresponds to the anterior border of the joint surface, while the straight line, as Figure 15-*D* shows, represents the posterior border, not the floor of the condyle, as Grashey describes it. This last view and others, which are not shown here, also demonstrate that the roentgenogram of the intercondyloid tubercles is produced by a summation of structures which lie in different frontal planes. The roentgenogram of the medial tubercle corresponds to a bony protrusion which lies on a more

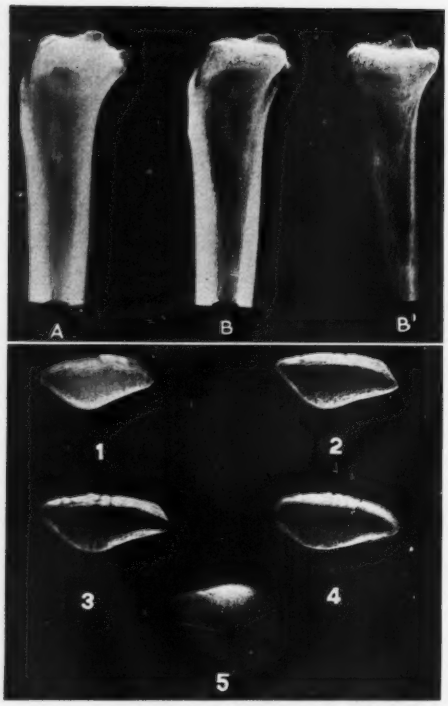


Fig. 16-*A* (*upper*). Profile view of the proximal end of a normal macerated tibia. In Fig. 16-*B* the bone has been divided into a lateral (*B*) and a medial (*B'*) portion.

Fig. 17 (*lower*). Roentgenograms of horizontal sections through the patella.

posterior plane than the one which is responsible for the view of the lateral. The postero-inferior border of the posterior intercondyloid fossa is delineated by an indistinct U-shaped line which is best visible in Figure 15-*D*, but which can be recognized also on other views.

PROXIMAL END OF TIBIA (PROFILE VIEW)

Direction of the x-ray beam: tibiofibular.

The profile view of the tibia does not contain many features which require special study and explanation. In our lateral view of the tibia (normal control Fig. 16-*A*), we see three nearly horizontal lines connecting the anterior and posterior borders of the bone in the condylar region corresponding to the articular surface. One of our sections, which divides the bone into nearly equal lateral and medial halves (Figs. 16-*B* and 16-*B'*), demonstrates the anatomical substrate of these lines. The sharpest line in the roentgenogram, Figure 16-*B*, which depicts the lateral half, represents the lateral infraglenoid margin of the tibia. In Figure 16-*B'*, showing the medial half of the tibia, we see two lines, an upper, interrupted by the medial intercondyloid tubercle, and a lower. The upper corresponds, as detailed comparison between bone sections and other roentgenograms (not shown here) prove, to the medial part of the condylar articular surface, the lower to the medial infraglenoid margin. All three lines are visible also on the control. As to the intercondyloid tubercles, we see from our figures that one is superimposed on the other. Detailed analysis shows that only their posterior contour produces partly separate delineation.

PATELLA

Horizontal sections at different levels demonstrate a thick anterior and a thinner posterior cortex which meet at the sides (Fig. 17). Enclosed in this shell of cortical substance is a trabecular meshwork, the individual tracts of which run mostly in an anteroposterior direction. Sections in sagittal planes confirm this (Fig. 18) and show that the anterior cortex is made up of densely arranged cephalo-caudad running trabeculæ (Joachimsthal). From these facts we recognize that a full face view of the patella (even if it is possible to obtain it free from the overlapping femur through oblique projection) will not yield much information in regard to the structure of the bone. The proportionally thick anterior cortex will, curtain-like, obscure many structural details. Roentgenograms of our frontal sections (Fig. 19) confirm this. Since the spongious structure is presented as a summation picture we can remove layers of bone without obtaining any change in the spongious arrangement. In Figure 19 comparison of the roentgenogram of the anterior half of the patella (*B*) with the roentgenogram of the posterior half (*B'*) shows the formermore

opaque than the latter due to the thickness of the anterior cortex. The spongious arrangement is alike in both views.

The lateral view will, therefore, give us more reliable information in regard to the spongious structure. Destructive foci involving the interior of the bone will show up on lateral view with greater probability since it is not obscured by a thick cortex. But here also the summation effect has to be taken into account. One fallacy should be pointed out. Since the trabecular arrangement normally is much looser in the apex of the bone, it should not be mistaken for a pathologic finding (Figs. 18-*A* and 18-*B*). A slight angulation of the posterior surface of the bone, visible on lateral view, is normal and corresponds to a horizontal ridge which divides this area into a superior and an inferior zone for articulation with the lower and upper parts of the trochlea of the femur in flexion and extension (Joachimsthal).

JOINT FISSURE

Since narrowing or widening of the joint fissure on the roentgenogram has been used as a diagnostic sign, it is important to realize the limitations of this symptom. Popovic and Doric have noted variations in the width of the fissure due to change in position. In a series of examinations they found that the space on the average is at least 1.5 mm. narrower in the upright than in the horizontal position. Swelling of the soft structures outside the joint will also lead to an apparent increase in the width of the joint fissure due to an increase in the distance of the object from the film. Direction of the x-ray beam, as well as the distance of the focus of the tube, from the film also plays a part.

Narrowing of the joint fissure on the injured side is supposed to be a sign of meniscus dislocation. In this respect a paper by Bauer is of interest. In a study of 150 knee joints he found in 58 per cent that the lateral part of the joint fissure was wider than the medial; in 14 per cent they were of equal width, while in 28 per

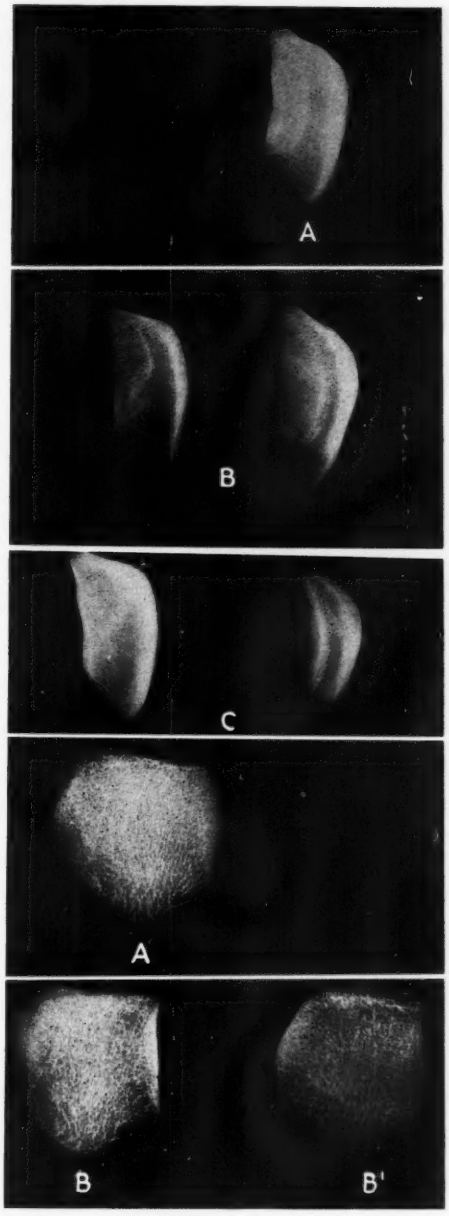


Fig. 18 (*upper*). Roentgenograms of serial sections through a normal macerated patella. *A*. Control. *B* and *C* depict sagittal sections through the same bone.

Fig. 19-*A* (*lower*). Roentgenogram of a normal macerated patella.

Fig. 19-*B* depicts the anterior half and *B'* the posterior half of the same patella.

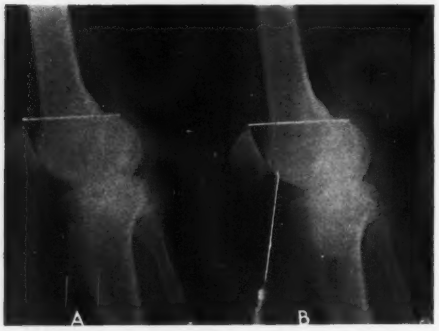


Fig. 20-*A*. Profile view of the knee joint of an unembalmed cadaver.
Fig. 20-*B*. The same knee joint after 40 c.c. of fluid have been injected. Note the increase in the distance between the two points connected by the line.

cent the medial was wider than the lateral. These differences were always equally marked on both knee joints of the same individual, if they were not diseased. Bauer comes to the conclusion that the width of the joint fissure does not have great importance in the diagnosis of an injury to the meniscus.

Another diagnostic sign which has been made use of frequently in a suspected injury to a meniscus, is a slight displacement of a femoral condyle in a lateral direction. Köhler has pointed out that this incongruity may not be due to an injury, but may be a sign of constitutional variation which, however, disposes to arthritis.

Hulten has made extensive studies on the relation of the intercondylar tubercles of the tibia to the femur. He found numerous variations, but points out that in extension the medial tubercle is always lateral to the medial condyle of the femur within the intercondyloid fossa, and the lateral tubercle directly underneath the lateral condyle of the femur.

Widening of the joint fissure and an increase in the distance between the patella and the femur has been used as a sign for intra-articular exudates. Taking into account the above-mentioned reservations, the rising of the patella from its bed on the femur, as seen on profile view of the knee joint, may be of value in ascertaining the presence of an exudate. In a group of experiments on unembalmed cadavers we tried to determine the amount of fluid necessary to produce a change in the position of the patella. While it may not be possible to come to definite conclusions with regard to inflammatory exudates *intra vitam* from our injection studies on cadavers, the results are nevertheless interesting. If we measured the distance between certain points on the patella and femur which can easily be identified, we found that an injection of an amount of fluid as small as 5 to 10 c.c. may produce a change in the distance of 0.1 cm., between these given points, injection of 20 c.c. increases the distance by 0.2 cm., 40 c.c. by 0.3 cm., 50 c.c. by 0.4 cm., 60 c.c. by 0.5 cm. (Figs. 20-*A* and *B*).

SUMMARY

1. A systematic analysis of the roentgenogram of the knee joint, which requires special technic, is presented.
2. The following experimental methods are used: chemical or mechanical removal of the cortical or spongious structures; serial sections of bones in planes perpendicular to the x-ray beam; production of small defects within cortex or trabecular structure or within both. Roentgenograms are taken at each stage of the different procedures.
3. The relative part of cortical and spongious layers in the production of the roentgenogram of the knee joint is demonstrated by various analytical experiments. Roentgenograms of the distal end of the femur are shown with either the cortical or the spongious part removed. Clinical implications in this connection are pointed out.
4. The spongiosal pattern in the roentgenogram does not correspond to single layers of bone trabeculæ, but represents a superposition of many strata of spongious bone which lie in the plane of the x-ray beam.
5. A separate study of the roentgenogram of the standard projections is undertaken by serial sections. This leads to an inter-

pretation of a number of details in the roentgenograms, not mentioned, or explained differently in the literature.

6. At variance with the literature are the findings in regard to Ludloff's spot; its distal anterior and posterior contours are formed by a narrow zone of intracondylar cortex and the increased transparency of the region is produced by the change in diameter of the cortex, especially thin in this region.
7. Attention is drawn to a number of normal findings on the femur, tibia, and patella which are often misinterpreted as pathologic, *e.g.*, the popliteal groove on the lateral condyle of the femur; processes in the area of the planum popliteum corresponding to the origin of the two heads of the gastrocnemius and plantaris muscles; limiting grooves on the inferior surface of the femoral condyles; translucent spots in the proximal part of the tibia and in the apex of the patella.
8. The limitations of the sign of narrowing or widening of the joint fissure in the roentgenogram are pointed out. In injection experiments on unembalmed cadavers with different amounts of fluid the rising of the patella from its bed on the femur is observed and measured on profile view.

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A COMPARISON OF GASTROSCOPIC AND ROENTGEN FINDINGS[1]

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THE flexible gastroscope has opened a new field in gastric diagnoses. In most cases it is safely and easily introduced and allows excellent visualization of the gastric mucosa in the living person. We have had three gastric perforations, all occurring during the use of instruments equipped with the spherical sponge tip devised by Henning. Experimental evidence indicates that the friction of this tip was responsible for these non-fatal accidents (9). No accidents have occurred when the long-finger guide was used. Lesions obstructing the esophagus and cardiac end of the stomach, aortic aneurysm, and suspected esophageal varices are contraindications to gastroscopy.

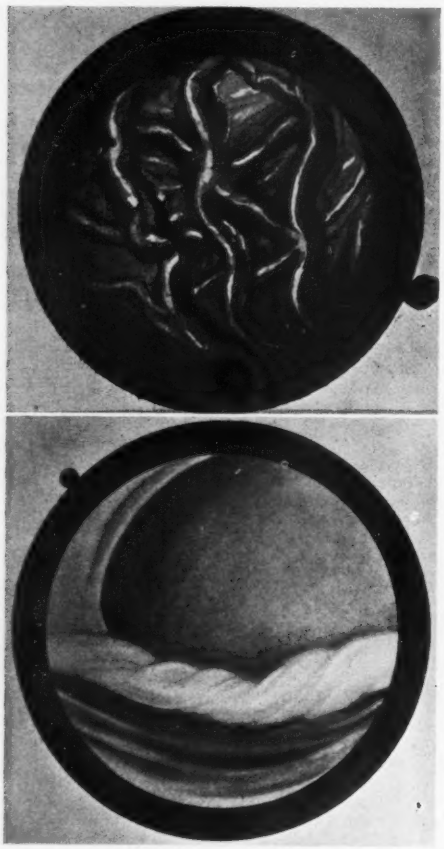

Fig. 1 (*above*). Gastroscopic appearance of the normal posterior wall of the body. There are parallel folds, bifurcated folds, and cross folds.

Fig. 2 (*below*). Gastroscopic appearance of the normal musculus sphincter antri and antrum. The twisted, rope-like fold separates the corpus (below) from the antrum (above). The curved structure extending upward from the left end of the musculus sphincter antri is a part of the gastric angle and obscures the superior portion of the foldless antrum.

Although most gastroscopists check their findings with roentgen findings, few radiologists check with the gastroscopist. Schatzki (8), Ansprenger (1), and Jutras (6) have made such comparisons. From 1926 to 1934 Sielman and Schindler made roentgenographic relief studies of the stomach in more than 4,000 cases. Of these cases, several hundred were gastroscoped. Since September, 1934, over 800 gastroscopies have been performed at the University of Chicago Clinics, most of these cases having been examined by Dr. Templeton by roentgen relief methods either before or after he had seen them gastroscopically.

Gastroscopic and roentgenologic examinations should be considered as cooperative rather than competitive examinations. Either method may visualize lesions that the other cannot. Shape, contour, motor function, and gross lesions are better seen roentgenologically, while mucosal changes and smaller lesions are better seen gastroscopically. In some cases the roentgenologic examination is sufficient for accurate diagnosis.

[1] Presented before the Radiological Society of North America, at the Twenty-second Annual Meeting, Cincinnati, Nov. 30–Dec. 4, 1936.

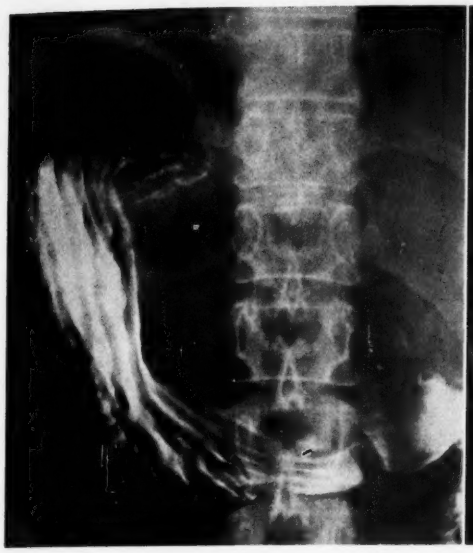

Fig. 3.

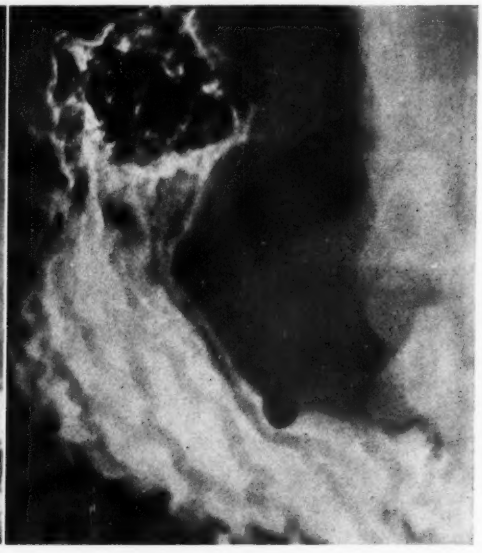

Fig. 4.

Fig. 3. Normal gastric rugæ. The folds tend to be parallel throughout the stomach and bulb. At the angle note the characteristic crossing-over of the folds from the lesser to the greater curvature. This appearance is presumably caused by a slight twisting of the antrum on the body.

Fig. 4. Normal gastric rugæ. The folds tend to be wavy and occasionally branch. The distance between the folds is quite wide.

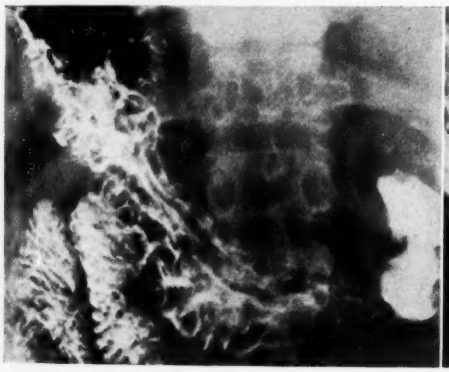

Fig. 5.

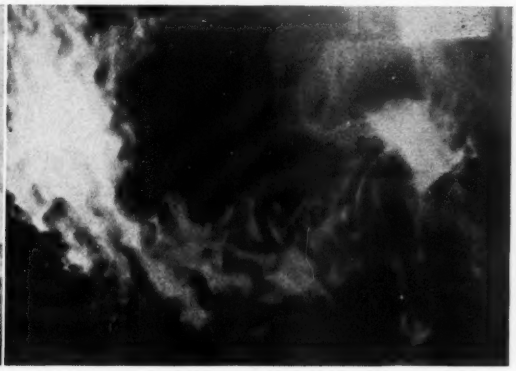

Fig. 6.

Fig. 5. Normal gastric mucosa. The polyp-like folds may be mistaken for gastric polyps or hypertrophic gastritis. Under the fluoroscope the folds were quite pliable and readily obliterated by pressure.

Fig. 6. Normal gastric rugæ. The prominent antral folds resemble the ridges seen in crumpled paper (Gutzeit). At gastroscopy no antral folds were seen. This stomach and those illustrated in Figures 3, 4, and 5 appeared very similar at gastroscopy. (See Figures 1 and 2.)

GASTROSCOPIC APPEARANCE OF THE NORMAL STOMACH

In the normal stomach, differences between the gastroscopic and the roentgenographic appearance are quite striking. Before the introduction of air the gastroscopist sees rather prominent, irregular, parallel folds which apparently do not correspond with the rugæ. This appearance of the collapsed mucosa presumably has nothing to do with its thickness and may or may not be of clinical significance. On distention with air these folds flatten easily and there appear in the body from 10 to 14

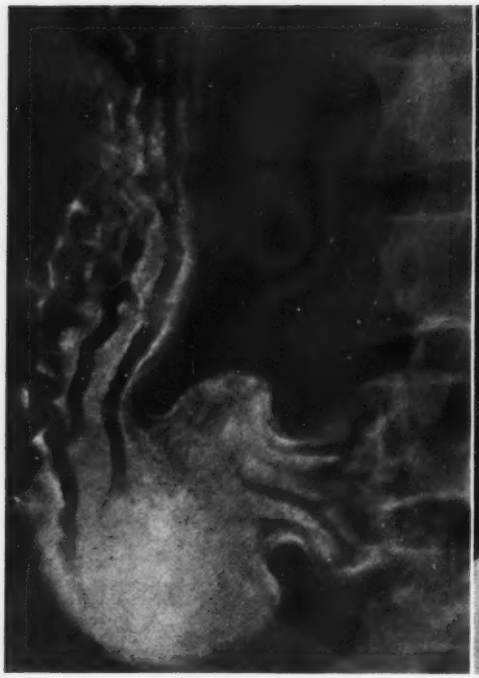

Fig. 7.

Fig. 8.

Fig. 7. Normal gastric rugæ in superficial gastritis. Four or five more or less parallel folds are seen in the body after a single swallow of barium mixture.

Fig. 8. Same stomach illustrated in Figure 7 after more complete filling and the application of a slight amount of compression. A dozen or more folds are now seen. The folds have not enlarged but the spaces between them have diminished. Although superficial gastritis was present, similar appearances and changes have been observed in stomachs which were normal at gastroscopy.

parallel folds, many of which are irregular, bifurcated, and traversed by cross rugæ (Fig. 1). Rugæ are rarely seen in the antrum, but a high-twisted cord-like structure separates the antrum from the body of the stomach. This fold, the musculus sphincter antri (Fig. 2), usually cannot be identified with certainty at roentgenologic examination.

ROENTGEN-RAY APPEARANCE OF THE NORMAL STOMACH

(*A*). *After a single swallow of barium.*—A variety of patterns may be seen (Figs. 3–6). Not uncommonly there are from four to six roughly parallel folds in the body and the antrum, and occasionally the antrum contains in addition one or more oblique folds.

(*B*). *After filling the stomach with barium and then compressing it.*—Now instead of the four to six folds originally seen, there may be from 10 to 14 (Figs. 7 and 8). Undoubtedly, the increase in number is to some extent explained by the entrance of barium into folds that were formerly pressed together or otherwise collapsed. Sometimes the parallel folds at the lesser curvature appear to split into pairs, while new folds appear as from nowhere. Several explanations have been suggested, but the fact is that many phases of the phenomenon are not understood.

CORRELATION BETWEEN ROENTGENOLOGIC AND GASTROSCOPIC APPEARANCES OF MUCOSA

In most cases the roentgenogram of the gastric mucosa bears little resemblance to the patterns seen by the gastroscopist, and sometimes changes clearly discernible at repeated gastroscopic examinations may be

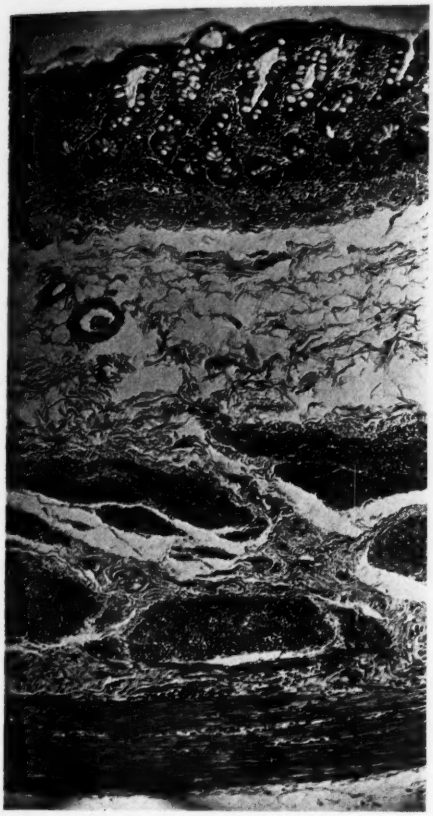

Fig. 9. Photomicrograph of a section through the gastric wall in a case of pernicious anemia. There is thinning of the mucosa with cellular infiltration and development of goblet cells. The submucosa is markedly increased in thickness.

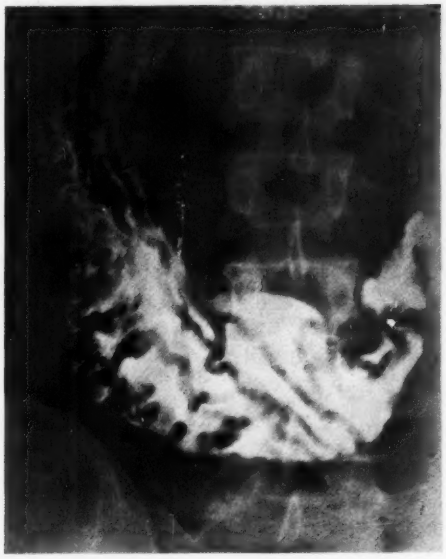

Fig. 10. Normal rugæ in severe hypertrophic gastritis. The swollen rugæ, erosions and small nodules seen between the folds at gastroscopic examination could not be demonstrated roentgenologically.

entirely indetectable by the roentgenologist. For example, there is the case of chronic ulcerative gastritis gastroscoped by Schindler in Munich on 65 occasions and followed over the same period by the roentgenologist, Sielman. During the period of observation Schindler noted the development of two sickle-shaped folds that crossed from the lesser to the greater curvature of the stomach and were interpreted as mucosal scars. Sielman, although convinced of the presence of the folds (on the basis of gastroscopic evidence), was unable to demonstrate the presence by any type of roentgen technic.

Conversely, the roentgenologist sometimes sees changes that are invisible to the gastroscopist. A case of gastric lymphosarcoma reported by J. F. Renshaw (7) illustrates the point. Both methods showed folds that were large before treatment and decreased in size following it. To the gastroscopist, however, it seemed that regression continued until the mucosa became completely normal, while to the roentgenologist there was definite evidence of persistence of an abnormal pattern of folds radiating from a point on the lesser curvature of the stomach.

The frequent failure of the gastroscopist to see radiating folds of the sort so often seen roentgenologically in cases of gastric ulcer suggests that these folds are not true rugæ but, instead, are wrinklings caused by changes in the submucosa or the muscularis. This may explain why roentgenologists sometimes see thickened folds in atrophic gastritis, a condition often marked by thickening of the submucosa beneath the atrophic mucosa (Fig. 9).

Obviously, gastroscopy is best suited to the study of the mucosa; roentgenology to the study of the deeper gastric tissues.

Fig. 11.

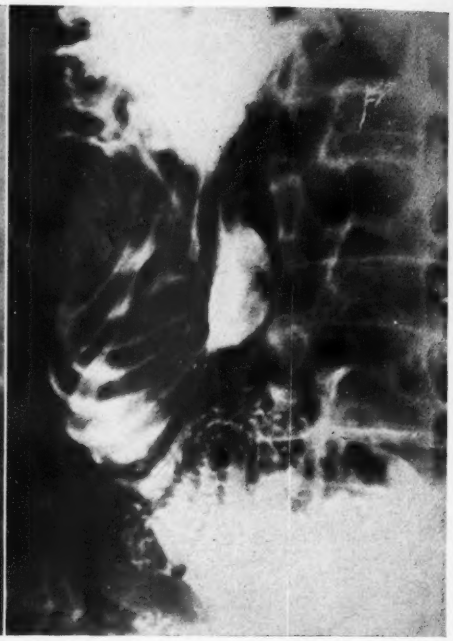

Fig. 12.

Fig. 11. Hypertrophic granular gastritis. At gastroscopic examination the folds appeared edematous and were covered with small nodules. At fluoroscopic examination the folds were rigid and could not be obliterated by pressure. Deep peristaltic waves progressed slowly through the entire stomach. The multiple small filling defects on the large folds in the central portion of the stomach are presumably caused by the small nodules seen at gastroscopic examination.

Fig. 12. Large benign ulcer before treatment. The crater seems to be in the lesser curvature in this view taken with the patient prone. With the patient supine, the ulcer appeared to lie in the posterior wall. The radiating folds, so prominent in the film, were not seen gastroscopically. Note the parallel rugæ of the anterior wall superimposed upon the radiating posterior wall folds.

GASTRITIS

Chronic gastritis is by far the most common disease of the stomach, and its practical significance is still underestimated. The diagnosis of this condition depends almost entirely on the gastroscopist who has no difficulty in seeing the superficial granules, nodules, crevices, hemorrhages, ulcerations, and mucosal edema (10). Also, the small hemorrhages, pigment spots, and hemorrhagic erosions present in stomachs prone to development ulcers are quite apparent. These lesions rarely, if ever, are seen with present roentgenologic technics (Figs. 7, 8, and 10). Schatzki (8), however, succeeded in demonstrating the erosions of ulcerative gastritis in one case.

In the past, many investigators believed that differences in fold thickness were diagnostic of inflammatory changes. Broad folds were assumed to be characteristic of hypertrophic gastritis, thin folds of atrophic gastritis. Experience has shown, however, that this conception was not entirely correct. Thick folds may be found in advanced atrophy and normal appearing folds in cases of hypertrophic gastritis. This bears out the finding of Henning who, as a result of his collaboration with Schatzki, found almost every type of fold in every form of gastritis (Table I).

Changes in fold thickness are not indicative of the state of the mucosa, and folds seen roentgenologically do not correspond to those seen gastroscopically or in the gross specimen. In certain cases, however, enormously enlarged folds which are difficult to obliterate with pressure are signifi-

Fig. 13.

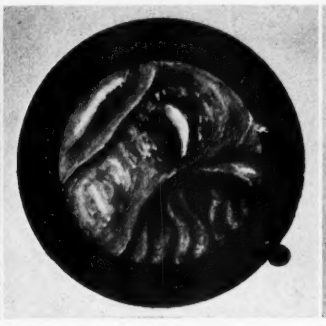

Fig. 14.

Fig. 15.

Fig. 13. Gastroscopic appearance of the ulcer shown in Figure 12. This large posterior wall ulcer illustrates the sharp edges indicative of benignity. The nodules in the floor are pancreatic lobuli. These lobuli probably caused the irregularity of the ulcer floor in the roentgenogram (Fig. 12).

Fig. 14. Gastroscopically the ulcer illustrated in Figures 12, 13, and 16 has reduced markedly in size after three weeks of treatment. There is some inflammation of the surrounding mucosa but the converging folds, observed roentgenologically, were not seen.

Fig. 15. Gastroscopic appearance of the antral polyp illustrated in Figure 17. An umbilication, not an erosion, is present in the center of the polyp. Smooth mucosa suggests benignity but such cases should be examined frequently because of possible malignant changes.

cant. Such cases probably have associated changes in the submucosa and muscularis.

Chronic hypertrophic gastritis in three out of 450, or about 0.7 per cent of our cases, is characterized roentgenologically by the appearance of small nodular filling defects or thickened infiltrated folds (Fig. 11). The fixed nature of these nodules produces a granular appearance that differentiates them from mucous flecks, small air bubbles, and food particles, all of which are free to move about under manipulation.

TABLE I.—THE DIFFICULTY IN THE DIAGNOSES OF THE VARIOUS TYPES OF GASTRITIS FROM FOLD SIZE IS EMPHASIZED. (*From Henning.*)

Roentgen Reports	Gastroscopically Found
Broad folds	1. Hypertrophic gastritis 2. Erosive gastritis 3. Atrophic gastritis 4. Normal picture
Normal folds	1. Normal mucosa 2. Hypertrophic gastritis 3. Atrophic gastritis
Small folds	1. Normal mucosa 2. Atrophic gastritis

Cases have been described by Brunn and Pearl (3), Berg (2), Gutzeit (4), and Weltz (11). Roentgenologic differentiation from submucosal infiltrating carcinoma, lymphosarcoma, and polyposis may be difficult. Deep, slowly progressing, peristaltic waves present in the three cases seen by us may be of differential diagnostic importance. On the other hand, some of the European investigators observed feeble peristalsis in this condition.

PEPTIC ULCER AND NEOPLASM

In most normal stomachs and most cases of pyloric neoplasm, the gastroscopist is able to see the pylorus, but quite commonly he cannot see this region in cases of duodenal ulcer or ulcer of the pyloric canal and pre-pyloric region. This is probably due to the fact that ulcerative lesions cause adhesions which displace the pylorus. An important diagnostic point is involved. If pyloric obstruction is present, the roentgenologist seldom has difficulty in demonstrating the fact, but he may be unable to differentiate between obstructing ulcer and neoplasm. In such cases, if the obstruction is malignant, the gastroscopist will probably be able to see into the pyloric antrum and observe the lesion directly. If he is not able to see into the pyloric antrum, this suggests that the pylorus is displaced by adhesions and, thus, speaks for a benign lesion.

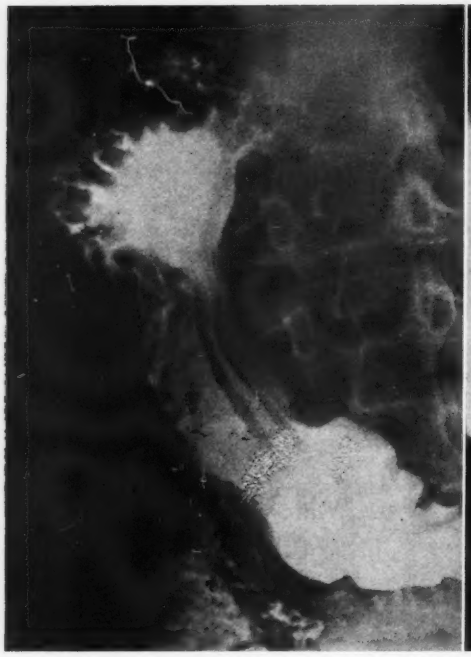

Fig. 16.

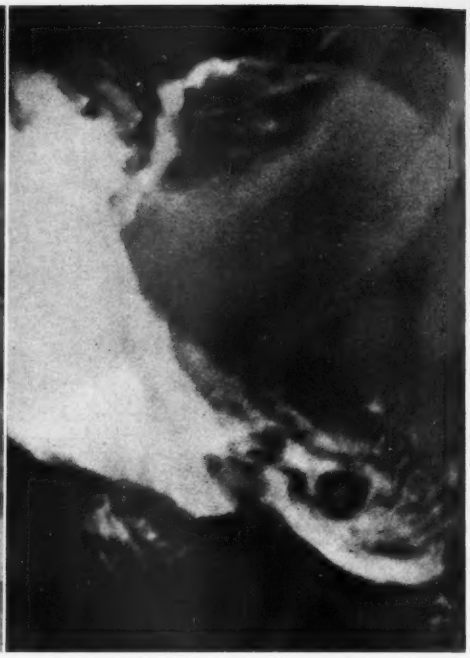

Fig. 17.

Fig. 16. After three weeks of medical treatment the ulcer, illustrated in Figure 12, has completely disappeared. A few radiating folds remain but are almost completely obscured by the overlying prominent anterior wall folds.

Fig. 17. Benign antral polyp. The rugæ spread to enfold the filling defect caused by the polyp. The patch of barium at the center of the defect undoubtedly lies in the umbilication seen gastroscopically (Fig. 15).

Ulcers along the lesser curvature of the antrum and occasionally in the body may not be seen by the gastroscopist even though they are readily seen by the roentgenologist. The ulcers along the lesser curvature of the antrum are often hidden behind the gastric angle (Fig. 2), while the ulcers in the body may be obscured by the inflammatory edema about the margin, may lie behind overlapping folds, or may lie in one of the two blind spots, namely, a small area about the esophageal orifice and a small area on the greater curvature where the instrument impinges.

It is rare for the gastroscopist to find an ulcer missed at roentgen examination. Most of these ulcers occur high on the lesser curvature or posterior wall or in the stoma of an anastomosed stomach. Occasionally ulcers missed at routine roentgen examination can be demonstrated once the location is known; others cannot be demonstrated regardless of the effort put forth.

The healing process of ulcers is usually best followed through the gastroscope. In a case gastroscoped 13 times, the ulcer had not epithelialized after three months of therapy although the crater had disappeared roentgenologically (Figs. 12, 13, 14, and 16).

Benign tumors, two centimeters or more in diameter, show well in relief roentgenograms (Figs. 15 and 17). The smaller polyps, seen in 2 per cent of the gastroscopies, are often missed roentgenologically. This fact suggests that the soft early carcinomatous tumors may be seen earlier by gastroscopy than by relief methods. Actually, however, both methods have equal value as very early carcinomas may sometimes be seen by either method.

In carcinoma, gastroscopy has two advan-

tages. It may be of greater value in determining the operability of a carcinoma as far as extent of involvement of the gastric wall is concerned and often permits definite differentiation between benign and malignant ulcer. Because of the latter fact, gastroscopy is necessary in ulcers occurring in patients over 35 years of age.

By means of gastroscopy carcinomas can be grouped into four morphological and clinical types. Type I is the broad-based, polyp-like, well-limited tumor. This is the type most amenable to resection. Type II is an area of ulceration sharply limited from surrounding normal gastric wall. This type, also, is susceptible to resection. In roentgenograms it produces the well-known "meniscus" sign. Type III is only partially limited and, therefore, operable only when it infiltrates toward the pylorus. Type IV is a diffuse infiltrating carcinoma which, in its earlier stages may be overlooked by either of the two methods.

Examination by the relief method should always be followed by examination of the barium-filled stomach. Sole reliance upon the relief method may result in a diagnosis of an early carcinoma which does not exist. Occasionally, gastric ulcers may not be seen or may be only suspected by relief technic, whereas the filled stomach leaves no doubt of their existence.

CONCLUSIONS

1. Roentgenograms and the gastroscope should be looked upon as co-operative rather than competitive means of studying the gastric mucosa.

2. Sometimes roentgenograms alone will establish the diagnoses but gastroscopy, as well, is often required.

3. Some of the differences that occur between gastroscopic and roentgenologic examinations are described and explanations are offered as to why these exist.

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THE VALUE OF GASTROSCOPY IN DIAGNOSIS[1]

By EDWARD B. BENEDICT, M.D., *Boston, Mass.*

From the Massachusetts General Hospital

GASTROSCOPY was first attempted by Kussmaul in 1868, the subject of the experiment having been a professional sword swallower. A rigid instrument was used, the lighting was indirect, and no view of the stomach was obtained. Mickulicz, about 1881, again attempted gastroscopy with a rigid instrument, but the results were unsatisfactory. Since 1900 gastroscopy with rigid instruments has been practised in a few clinics, principally in Germany, but most physicians have felt that for diagnostic purposes the results obtained did not justify the difficulties and dangers encountered in passing the instrument. The invention of the Wolf-Schindler flexible gastroscope (1) has made possible the frequent and general use of gastroscopy in diagnosis. The flexibility of this new instrument, invented by Dr. Schindler in 1932, has made the procedure relatively easy and safe. In a series of 400 gastroscopies performed at the Massachusetts General Hospital since 1933, I have had only one complication. This occurred in one of my early gastroscopies as a result of over-inflation of the stomach with air. A pin-point perforation followed, and a sterile pneumoperitoneum. Operative interference was unnecessary, but about ten days later, as the nitrogen in the peritoneal cavity had not been absorbed, it was released through a one-inch abdominal incision.

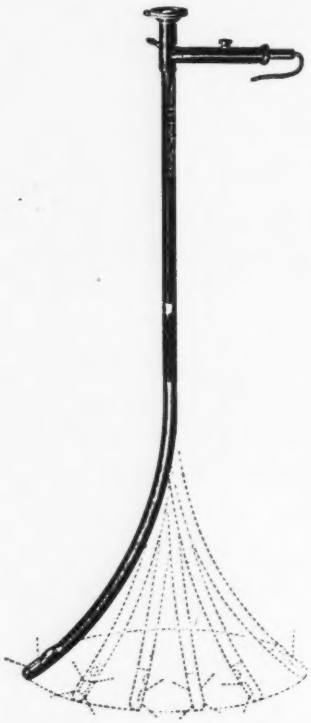

Fig. 1. The Wolf-Schindler flexible gastroscope.

Gastroscopic examination is, of course, carried out with the stomach empty; codeine or morphine is given to aid relaxation, and atropine is used to diminish excessive salivation. Local analgesia of the throat is produced by the application of a solution of 2 per cent pantocain. The patient is placed on the left side of the examining table, with the head extended on pillows or held in the hands of a trained assistant. With the fingers of the left hand as a guide, the gastroscope is then introduced into the esophagus, and by very gentle pressure on into the stomach. A small amount of air is blown into the stomach through the sheath of the instrument, for without air space the walls of the stomach are collapsed and no satisfactory view is obtained. Orientation is accomplished by knowing the approximate depth of in-

[1] Read by invitation at the Twenty-second Annual Meeting of the Radiological Society of North America, in Cincinnati, Nov. 30–Dec. 4, 1936.

troduction, and by an indicator on the ocular which shows the direction toward which the objective lens is rotated.

The chief value of gastroscopy is in the study of the finer changes in the gastric mucosa. X-ray examination is very accu-

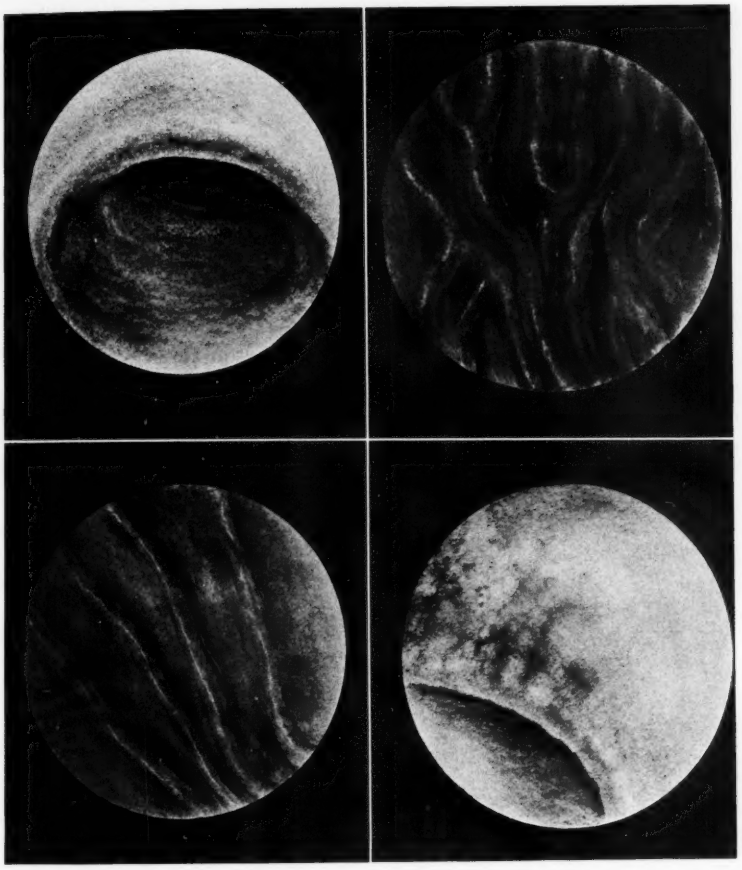

Fig. 2 (*upper left*). Normal pylorus.
Fig. 3 (*upper right*). Normal greater curvature. Note normal rather large rugæ.
Fig. 4 (*lower left*). Normal lesser curvature. Comparatively small rugæ.
Fig. 5 (*lower right*). Hypertrophic gastritis. Typical verrucous appearance of the mucosa on the lesser curvature near the angle of the stomach.

The appearance of the normal pylorus is shown in Figure 2. In the normal stomach regular peristaltic waves are seen passing over the antrum and ending with a tight closure of the pyloric sphincter. Rugæ are usually not seen in the antrum by gastroscopy. The next drawing (Fig. 3) shows the normal greater curvature where the rugæ are quite large. On the lesser curvature rugæ are small, as shown in Figure 4, or may be entirely absent.

rate in the diagnosis of peptic ulcer and neoplasm, and with the perfection of the relief method the roentgenologist is now studying the smaller lesions of the stomach. Here, however, the gastroscopist has the advantage of being able to look directly at the gastric mucosa and examine it in great detail in its natural color. Such gastroscopic study in no way lessens the necessity for x-ray examination, but is nevertheless an important additional diagnostic method.

Gastroscopy is of the greatest value in chronic gastritis (2), for in this disease the changes in the mucosa are smaller than in ulcer and cancer, and, therefore, are less easily recognized by x-ray examination. That chronic gastritis is a definite disease cannot be denied, for although the term has been loosely used in the past, we now have clinical, gastroscopic, roentgenologic, and pathologic evidence of its existence. Why, indeed, should anyone deny the existence of chronic gastritis, when in all other parts of the gastro-intestinal tract such diagnoses as stomatitis, esophagitis, duodenitis, enteritis, ileitis, colitis, and proctitis are generally accepted? The clinical diagnosis of chronic gastritis is unsatisfactory, for all investigators agree that the symptomatology is variable. Patients with chronic gastritis may have symptoms suggestive of ulcer, carcinoma, or neurosis. Gas, fullness, anorexia, heartburn, epigastric distress or pain, nausea, vomiting, and hematemesis may all occur in patients with negative x-ray examination. In some of these patients x-ray study may suggest gastritis; in many of them gastroscopy will demonstrate chronic gastritis. Dr. Schatzki in his presentation will give the x-ray evidence of chronic gastritis, while the gastroscopic appearance of gastritis will follow shortly in this paper. Pathologically, gastritis is diagnosed by edema, leukocytic infiltration, increase in the number and size of the lymph follicles, degeneration of the glandular epithelium, and erosions of the mucous membrane.

The typical gastroscopic appearance in hypertrophic gastritis is shown in Figure 5. Note the verrucous appearance of the mucosa on the lesser curvature near the angle of the stomach. Such small elevations are characteristic of the mucosal hyperplasia seen in chronic hypertrophic gastritis and are not visible by x-ray. Increased reddening and edema are also important evidence of inflammation as seen gastroscopically. Along the greater curvature in the same case (Fig. 6) the rugæ are somewhat prominent and tortuous, with alternate widening and narrowing, sometimes giving a bulbous or beaded appearance. Some of the folds show increased reddening along their crests. In this case x-ray examination showed slight enlargement of the rugæ, interpreted by Dr. Schatzki as evidence of inflammation in the mucosa. In another case (Fig. 7), however, we see by gastroscopy the characteristic beaded verrucous appearance of the mucosa in hypertrophic gastritis, yet the rugæ are small or absent and the x-ray examination was negative. Before gastroscopy this patient was thought to have a gastric neurosis. Gastroscopy here, as in other cases in which the diagnosis was not clear, has established a positive diagnosis of hypertrophic gastritis.

In chronic gastritis with erosions the gastroscope is also indispensable. A patient may come in with hematemesis or melena or both; x-ray examination of the stomach, duodenum, and colon is entirely negative. What is the source of the bleeding? Gastroscopy will frequently reveal erosions in the mucosa as shown in Figures 8, 9, and 10. Such erosions frequently occur on the crests of the rugæ, are only exceptionally visible by x-ray, and are undoubtedly the cause of bleeding in many cases.

Atrophic gastritis (3) is a disease seen chiefly in deficiency states, particularly pernicious anemia. X-ray examination may show small rugæ, but the diagnosis depends on gastroscopic examination. The characteristic appearance of the gastric mucosa in severe untreated pernicious anemia is shown in the illustrations (Figs. 11 and 12). Note the very pale mucosa, complete absence of rugæ, and network of blood vessels clearly visible shining through the thin mucosa. After liver therapy there is a tendency for the mucosa to improve (Fig. 13). The color has partly returned, blood vessels are no longer visible, and a few rugæ are now present.

Gastroscopy is also useful in gastric ulcer. X-ray examination is, of course, usually very accurate, and may demonstrate ulcers which are not found by gastroscopy. On the other hand, there are cases

in which a small ulcer is visible by gastroscopy and x-ray examination is negative. The gastroscopic appearance of benign

Fig. 6 (*upper left*). Hypertrophic gastritis. Same patient as shown in Figure 5. Note alternate widening and narrowing of rugæ.
Fig. 7 (*upper right*). Hypertrophic gastritis. Verrucous beaded appearance.
Fig. 8 (*lower left*). Small erosion on crest of tortuous fold.
Fig. 9 (*lower right*). Large superficial erosion on crest of wide fold in patient with otherwise unexplained hemorrhage.

ulcer is shown in the illustration (Fig. 14). Note the smooth, red, clean-cut margins, and clean base, indicating its benign character. In Figure 15 a small benign ulcer is seen in its healing stage. These ulcers were also seen by x-ray. In Figure 16, however, gastroscopy demonstrated a small ulcer high up on the posterior wall near the cardia. This ulcer was not seen by x-ray examination.

In the differential diagnosis of gastric ulcer and carcinoma direct observation of the lesion by gastroscopy has been helpful. In a recent patient the x-ray report was as follows: "The stomach contained some secretion at the beginning of the examination, and there was marked prominence of its rugæ throughout. Peristalsis began high on the greater curvature and passed without interruption to the pylorus. On the lesser curvature, however, there was no peristalsis distal to the angle of the stomach. Lying on the lesser curvature, just below the angle of the stomach, there was a 3-cm.-broad, shallow ulceration, with some thickening in the surrounding gastric wall. The walls of the stomach in this region were pliant throughout, and although peristalsis failed to pass over it, there was no evidence of rigidity. The patient complained of tenderness directly

over the lesion, but a definite mass could not be palpated. The findings are those of a definite lesion on the lesser curvature of the stomach just below the angle, the appearance of which is rather unusual. Taking the history into consideration, it seems possible that the patient may have an acute infection in the stomach wall at this point, with a shallow ulceration. The findings could also be due to an early benign peptic ulcer. Malignancy seems least likely but cannot be definitely excluded." Gastroscopy done two days later helped very materially in the differential diagnosis showing on the lesser curvature at the angle of the stomach "a grayish shallow lesion about 0.5 cm. in diameter, which appeared to be a benign healing ulceration." Four months later this patient was entirely symptom-free on medical treatment.

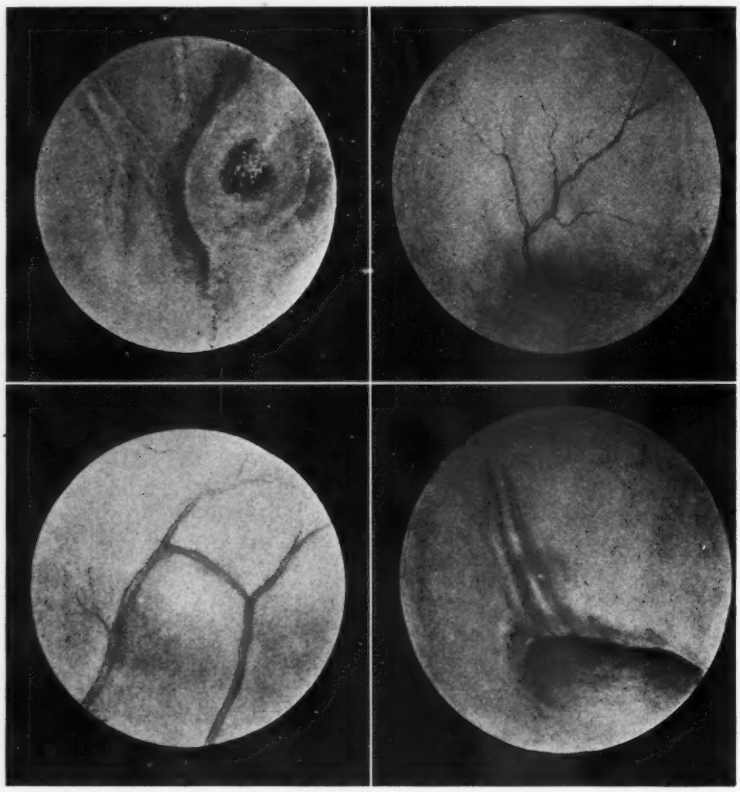

Fig. 10 (*upper left*). Large superficial erosion on bulbous fold. Such erosions may be the cause of severe bleeding.

Fig. 11 (*upper right*). Atrophic mucosa seen in untreated pernicious anemia. Note pallor, absence of rugæ, and network of blood vessels shining through the thin mucosa.

Fig. 12 (*lower left*). Atrophic mucosa in another patient with untreated pernicious anemia. See Figure 11.

Fig. 13 (*lower right*). Gastroscopic appearance of mucosa in pernicious anemia after liver therapy. Same patient as shown in Figure 12. Note improvement in color and rugæ.

In five patients during the last two or three years the question of lymphoblastoma of the stomach has been raised by x-ray examination, and although the roentgenologist himself often considered it an

unlikely diagnosis, gastroscopy has given reassurance that lymphoma was not present. In these cases gastroscopy has either been negative or has shown hypertrophic gastritis. The subsequent course of these patients has been against lymphoblastoma.

Gastroscopy is also useful in carcinoma of the stomach (4), in spite of the fact that here roentgenology is highly accurate. The typical nodular gastroscopic appearance of proliferating carcinoma is shown in Figure 17. In malignant disease gastroscopy may aid in confirming the x-ray diagnosis and may add valuable information regarding the extent and probable operability of the growth. For example, take the following x-ray report: "The stomach is unusually high in position, very small, and empties rapidly. As barium enters the stomach it is retained in the upper one-third until there is a moderate degree of distention of the fundus. Barium then passes over what appears to be an annular constriction which involves about one-half of the stomach. This constriction has the general appearance of a scirrhous carcinoma. Palpation and the usual type of examination was not possible, due to

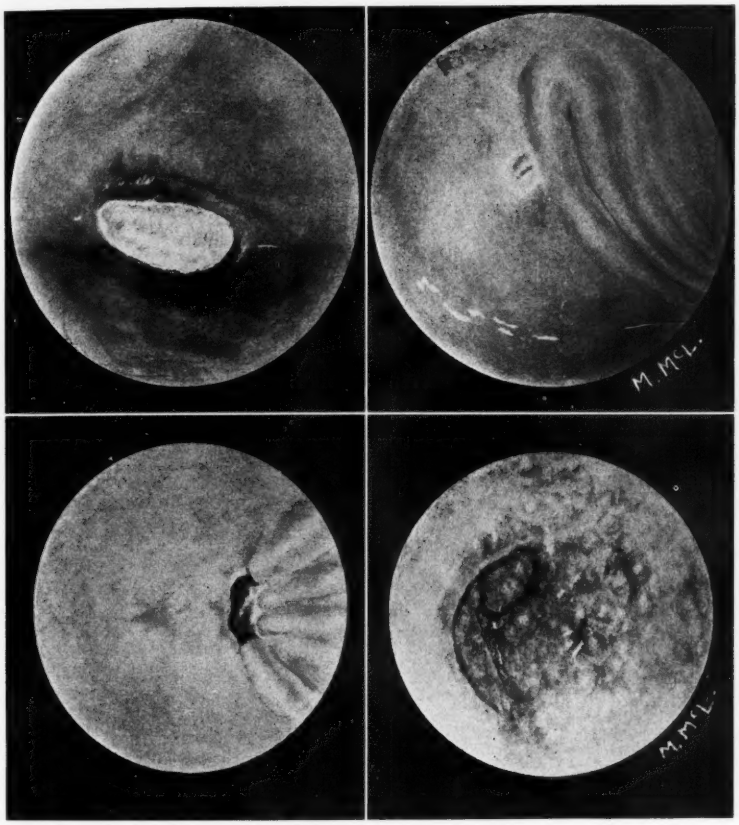

Fig. 14 (*upper left*). Benign gastric ulcer as seen by gastroscopy. Its benign character is indicated by smooth clean-cut margins and clean base.

Fig. 15 (*upper right*). Benign ulcer—healing.

Fig. 16 (*lower left*). Small benign ulcer high up on posterior wall near the cardia. This ulcer was the cause of severe bleeding and was seen by gastroscopy but not by x-ray.

Fig. 17 (*lower right*). Typical nodular gastroscopic appearance of proliferating carcinoma.

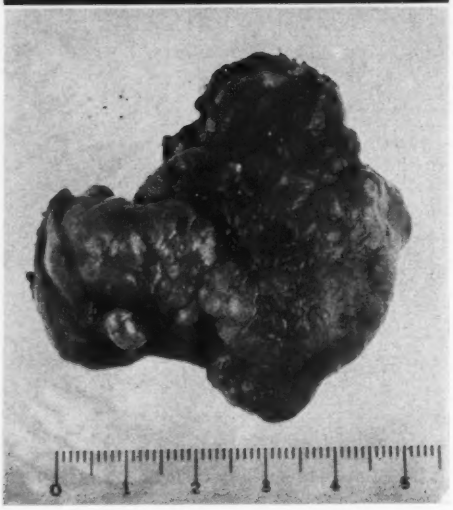

Fig. 18 (*upper*). Polypoid lesion of stomach as seen by gastroscopy. Same patient as shown in Figure 11. This polyp, when very small, was first seen by gastroscopy 22 months ago, but not confirmed by x-ray. Now very definite by gastroscopy and confirmed by x-ray. Resection Nov. 27, 1936. Pathologic report: adenocarcinoma, Grade I. (Note also improvement in color of mucosa and rugæ after liver therapy.)

Fig. 19 (*lower*). Photograph of resected tumor shown in Figure 18.

inaccessibility of the stomach. Syphilis could produce the picture." Gastroscopy in this case was of definite assistance in diagnosis. No normal mucosa was seen. The entire mucous membrane appeared studded with nodular protuberances which seemed to extend almost to the cardia. It was felt by gastroscopy that the lesion was malignant, with infiltration of most of the upper part of the stomach. Exploratory laparotomy a few days later showed four-fifths of the stomach involved in newgrowth, which was inoperable, both because of its local size and fixation, and because of metastases. Biopsy from a mesenteric gland showed metastatic adenocarcinoma.

In the early diagnosis of neoplasm gastroscopy may be of great importance, as shown by the following case. In January, 1935, a patient with pernicious anemia was examined by gastroscopy; marked atrophy of the mucosa was noted, with blood vessels shining through, as shown in Figure 11. In this patient, however, "on the greater curvature, near the antrum, there was a definite nodular protuberance about 2 cm. long and 1 cm. wide and raised above the mucosa about 0.5 cm. The surface of this appeared smooth, but there seemed to be two or three distinct nodules merging together." X-ray examination six weeks later was reported as follows: "Stomach is normal in position and outline. Its rugæ showed some prominence, but no definite polypi could be demonstrated. Duodenal cap and loop appeared normal. Findings are those of moderate prominence of the gastric rugæ. No other evidence of organic disease noted." One week later gastroscopy was repeated and again showed the protuberance previously noted. The mucosa in general, however, showed an improvement in color and rugæ formation as a result of liver therapy, and it was decided to observe this patient longer on liver treatment in order to determine whether the condition was true polyp or perhaps a pseudo-polyposis, in which case there might be improvement on liver therapy. Nine months later gastroscopy again showed a small polypoid lesion, which appeared smooth and non-malignant. Eleven months then elapsed before the fourth gastroscopy, which showed a very marked increase in the size of the polyp, as shown in Figure 18. From previous experience with polypoid lesions of the stomach (5) it was felt that this tumor was probably malignant. X-ray examination

now confirmed the gastroscopic findings, and a review of the films taken 22 months previously showed that the lesion should probably have been demonstrated by x-ray at that time. At operation the lesion was resected. The appearance of the pathologic specimen is shown in Figure 19. The pathologic report was adenocarcinoma, Grade I.

CONCLUSIONS

Gastroscopy is a valuable diagnostic aid in diseases of the stomach. It should not be used as a substitute for x-ray examination, but should be employed as an adjunct to it.

While gastroscopy is of great assistance in the diagnosis of small shallow ulcerations, in the differentiation of benign from malignant lesions of the stomach, in the early diagnosis of carcinoma, and in the observation of neoplasm with regard to its extent and operability, its chief field of usefulness lies in the study of the finer changes in the gastric mucosa, as in superficial, hypertrophic, and atrophic gastritis.

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THE COMPARATIVE VALUE OF GASTROSCOPY AND ROENTGEN EXAMINATION OF THE STOMACH[1]

By RICHARD SCHATZKI, M.D., Department of Roentgenology, Massachusetts General Hospital, *Boston*

IN the first half of this paper the roentgen appearance of the inner surface of the stomach as it is seen in the normal and in some pathologic conditions will be briefly reviewed, before discussing in the second half the comparative advantages of gastroscopy and roentgenology (2). The conclusions which will be drawn are based on seven years of close co-operation with gastroscopists (Dr. N. Henning, of Leipzig, and Dr. E. B. Benedict, of Boston).

Only a few words may be said about the well known picture of the normal gastric folds. They are soft and fairly straight on the anterior wall, more rigid and tortuous toward the greater curvature as well as in the fundus and on the posterior wall. The rugæ are formed by both mucosa and submucosa, a fact which should be kept in mind when interpreting pathologic conditions.

How does this picture change in gastritis? Does it change at all? These questions cannot be answered categorically. There are cases in which the roentgen film shows marked changes. The rugæ differ from those of the normal stomach; they are wider and higher. They are also more rigid, and one cannot make them disappear by pressure. All these changes indicate an increase in the thickness of those structures which form the rugæ, *i.e.*, the mucosa and the submucosa.

The thickness of the folds prompted the name of "hypertrophic gastritis" for these cases. It does not correspond exactly to what the gastroscopist means when he speaks of hypertrophic changes. *He* thinks of the hypertrophic new formations of the mucosa itself, like warts or polyps, changes which—on account of their size—are rarely demonstrable by roentgen examination.

There are roentgen signs aside from the appearance of the rugæ which characterize gastritis, such as increased gastric secretion and small round areas of diminished density which are due to particles of mucus (Berg). One should hesitate to make the diagnosis of hypertrophic gastritis in the absence of this type of secretion; in other words, to make the diagnosis of gastritis in a dry stomach.

What does the gastroscopist see in cases like those just mentioned? If the changes are typical by x-ray he almost invariably finds gastritis, usually with marked hypertrophic warty changes of the mucosa. In rare instances, however, no gastritic changes are found by gastroscopy, and even atrophy may be present in exceptional cases.

Extensive degrees of hypertrophic gastritis may simulate cancer, as was emphasized by Cole. This is particularly true of cases with localized hypertrophic changes. By rotating the patient, it is usually possible to demonstrate the rugal character of the swelling and sometimes the transition of the swollen into the normal part of the rugæ. The possibility of the so-called "congenital giant rugæ," as described by Scherer and by Windholz, has to be considered in such cases.

A discrepancy between roentgen findings and gastroscopy is as a whole rather rare when changes typical of hypertrophic gastritis are demonstrated by roentgen examination. The converse is much more common. A large number of patients with an appearance of hypertrophic gastritis by gastroscopy show a normal roentgen picture. The changes in these cases ap-

[1] Presented before the Radiological Society of North America at the Twenty-second Annual Meeting, at Cincinnati, Nov. 30–Dec. 4, 1936.

[2] The literature will not be quoted in detail. See papers in bibliography for extensive references.

parently involve the mucosa more than the submucosa. In other words, a negative roentgen examination does not exclude gastritis, whereas positive roentgen findings are usually more conclusive if interpreted with care and self-criticism.

Much more unsatisfactory is the roentgen diagnosis of *gastric atrophy*. Not infrequently, one may see the expected thinning of the rugæ, *e.g.*, in cases of pernicious anemia. The relief picture, however, may appear completely normal, though gastroscopy shows marked atrophy. On the other hand, I have seen stomachs with extremely thin rugæ in cachectic persons, *e.g.*, in a series of patients with advanced pulmonary tuberculosis, without there being the least evidence of atrophy by gastroscopic examination or functional tests (6). The thin rugæ in these cases are, therefore, not due to local disease of the mucosa but probably caused by dehydration of the entire body with consequent shrinking of the submucosa.

Taking everything into consideration, it is not possible to diagnose atrophy of the gastric mucosa conclusively by roentgen examination.

It was also thought that the third form of gastritis, the *ulcerative gastritis*, could not be demonstrated by the x-ray. This type is characterized by very shallow superficial erosions. A few years ago I succeeded for the first time, after several futile attempts, to obtain roentgen films of this condition, after it had been discovered during gastroscopy (5). Films were taken during fluoroscopy with measured pressure which showed numerous shallow ulcerations at the crests of the rugæ. Each of these ulcerations was surrounded by an edematous wall. Two months later, after medical treatment, the erosions had disappeared. They could not be found either by x-ray examination or by gastroscopy. This case, however, represents an exception. The shallowness of the erosions and the marked degree of accompanying gastric secretion usually prevent their demonstration.

Only a few words may be said in regard to the possibilities of the roentgen demonstration of gastric tumors. Small tumors can be recognized as such even though their size may barely surpass the width of a gastric fold.

The exact delineation of the tumor is of great importance to the surgeon. The changes of the relief picture of the stomach coincide closely with the intragastric extent of the tumor. Multiple tumors can be separated and recognized as such.

This résumé of the roentgenologic possibilities seemed necessary before giving a comparison of the advantages and disadvantages of gastroscopy and x-ray examination of the stomach. This will naturally represent my own experience which, as mentioned before, is based on seven years of close co-operation with gastroscopists.

First, something may be said about the advantages of gastroscopy. It is certainly superior to x-ray from the purely optical standpoint. It is done with precise instruments, such as lenses and mirrors, giving the same optical impression as the naked eye would have. It is even superior to this, as it gives a slightly magnified picture. Roentgenograms are comparatively crude pictures, considering the grain of the contrast meal, of the film, and the screen, and other obvious limitations.

The conclusion must be that gastroscopy is superior to x-ray examination in the diagnosis of minute changes of the inner surface.

Another advantage of gastroscopy is the ability to see colors. Roentgen diagnosis is based only on differences in the level of the crests and valleys of the inner surface, whereas gastroscopy has this additional help of difference in color.

Roentgenology, on the other hand, possesses other advantages. There are at first some practical ones. It is easier and still less dangerous to do an x-ray examination than to do a gastroscopy. X-ray is, therefore, more fit for routine clinical work.

Moreover, it is possible to demonstrate all portions of the stomach by x-ray examination, whereas it is difficult, sometimes even impossible, to see certain parts of the

stomach by gastroscopy, *e.g.*, parts of the fundus or of the lesser curvature of the antrum. Roentgenology is, therefore, superior to gastroscopy in cases in which it is necessary to search every corner of the stomach in order to demonstrate a circumscribed, not diffuse, lesion.

Roentgenology is further superior to gastroscopy in regard to the description of the extent of a lesion, as the endoscope rather often can demonstrate only its upper margin, although it may sometimes do this more accurately than the x-ray examination.

There is, finally, a more important advantage of x-ray, *i.e.*, the routine observation of peristalsis of the whole stomach as well as the impression obtained by manual palpation which gives information concerning flexibility or rigidity of the wall. In other words, roentgenology is superior in the demonstration of the processes in the deeper layers of the stomach wall.

If one applies the principal differences of the two methods to their diagnostic possibilities in the various lesions of the stomach, one comes to the following conclusions:

(1) *Concerning gastritis:* There are cases in which it is possible to make a definite diagnosis of gastritis by x-ray. There are, however, a large number of cases of gastritis which are completely negative by x-ray. Gastroscopy is, therefore, by far the best method of examination for the diagnosis of gastritis.

(2) *Concerning ulcer:* It is usually easier to discover *large* ulcers by x-ray and to describe their size and position.

A control gastroscopic examination of the surrounding surface and of the crater base for the question of malignant degeneration may be of great importance, however.

Ulcers, which on gross examination by the pathologist appear benign but prove to be malignant by microscopic examination, cannot be diagnosed as such by any method of macroscopic examination.

Small ulcers of the stomach may be easily overlooked by x-ray examination. It may be even impossible to see a small ulcer by the x-ray though the exact localization is known by a preceding gastroscopy. On the other hand, ulcers, definite by x-ray, may be overlooked by gastroscopy, or it may be impossible to bring them into the field of the scope.

I have seen examples of both possibilities, and I think that the efficiency of both methods is about the same in this regard.

Healing of gastric ulcers, indicated by a decrease in size and shape of the niche and later the formation of the "rugal star," can be well followed by roentgen examination. There is, however, no doubt that gastroscopy is superior in regard to the observation of the final healing process of the mucosa.

(3) *Concerning tumors of the stomach:* The diagnosis of tumors of the stomach, including cancers, is usually much easier and more certain by x-ray.

A gastroscopic control, however, may be of utmost importance if there is any question about the nature of a small tumor-like defect (such as, when there is a question of tumor or unusual mucosal fold), or if we are dealing with the differential diagnosis between hypertrophic gastritis and diffuse cancerous or lymphoblastomatous infiltration, a decision which may be extremely difficult by x-ray examination. The similarity between these lesions may be so great that even the direct visualization of the lesion through the gastroscope may not lead to a definite diagnosis. I have seen the diagnosis of malignancy made by gastroscopy in a few cases of gastritis.

The help which gastroscopy offers in the differential diagnosis of intrinsic and extrinsic lesions of the stomach in difficult exceptional cases cannot be over-estimated.

Finally, it is worth-while to mention the fact that gastroscopic control may correct obvious mistakes in x-ray examination and interpretation.

Summarizing, if one should be asked to renounce either gastroscopy or roentgenology, one would without doubt prefer to keep roentgenology, but the question is wrong in itself. Gastroscopy is an important supplementary method. A diagnostic

problem may be difficult to solve by roentgenology and may be no problem at all for gastroscopy and *vice versa*. The correlation of the findings by the two methods has increased our knowledge of the normal and diseased stomach and has helped us in many individual cases.

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RELATIVE MERITS OF GASTROSCOPIC AND ROENTGENOLOGIC EXAMINATION

By B. R. KIRKLIN, M.D., *Rochester, Minn.*

Section on Roentgenology, The Mayo Clinic

AT the outset I wish to insist strongly that if there is any rivalry between roentgenologic and gastroscopic methods of examination, it is altogether friendly. If the gastroscope will disclose and identify lesions that escape roentgenologic revelation and recognition, then by all means let it come into more common use. Any method that makes for a closer approach to accuracy in diagnosis deserves a hearty welcome. In this instance, however, the margin for potential improvement is narrow, for in competent hands, such as are available almost everywhere, the roentgen ray will disclose at least 95 per cent of lesions that could be seen by direct inspection, and will permit a specific diagnosis of most of them.

The gross lesions, including the advanced cancers and benign newgrowths, have such striking roentgenologic characteristics, demonstrable even by the simplest technics, that few errors in diagnosis are permissible. It is true that the primarily benign tumors often contain malignant cells, but as a rule, a painstaking microscopic search is necessary to reveal these cells, and it is scarcely conceivable that they could be discovered by gastroscopic inspection.

But the efficiency of roentgenologic examination is not confined to gross lesions. By coating the mucosal surface of the stomach with a thin layer of barium at the beginning of the examination, as is commonly done, exceedingly small lesions can be exhibited roentgenoscopically and usually thus identified. To the adjunctive roentgenographic feature of this procedure the term "compression technic" is now applied and those who are uninformed are inclined to suppose that the method is fundamentally new. As a matter of fact employment of a thin coating for roentgenoscopy was introduced by Holzknecht in the early days of roentgenologic gastro-intestinal diagnosis, and has long been part of the standard routine. Further, roentgenoscopic inspection is practically indispensable to disclose and localize lesions prior to applying compression roentgenography, which also is in common use, chiefly for the preservation of a record.

By coating the mucosa with a thin layer of the opaque medium any gastric lesion, whether ulcerative or tumefactive, that visibly alters the internal topography of the stomach is demonstrable even when the diameter of the lesion is only a few millimeters, and any failure to find it should be charged against the examiner, not against the method. Minute ulcerating carcinomas can confidently be diagnosed as such, for the meniscus sign complex produced by the slight elevation of the crater margin is pathognomonic. Yet often in such instances the surgeon, after he has opened the stomach and exposed the lesion to view, is unable to say whether it is benign or malignant, nor after its removal can the pathologist determine its character by macroscopic inspection. It has been claimed that the gastroscopist can make this distinction in every case, but if this is true I cannot understand why an experienced surgeon looking closely and directly at these small ulcerating carcinomas is often unable to distinguish them from benign ulcers.

Similarly, malignant ulcer without any marginal tumefaction sometimes betrays its character roentgenoscopically by the irregular profile of its crater, but the irregularity would scarcely be detectable in the gastroscopic face view. As for the malignant ulcers that have the macroscopic appearance of benign ulcers and cannot be identified by the roentgenologist, or macroscopically by the surgeon or

pathologist, I fail to see how they could be recognized by the gastroscopist. In short, roentgenologic examination is almost as reliable as macroscopic inspection in determining whether a gastric lesion is malignant or benign. If the gastroscope can excel the roentgen ray or the unaided and unhampered eye in this regard, it will be useful indeed.

Not for a moment do I contend that the roentgenologic method is infallible or that it has no limitations. Some of the limitations I have already pointed out, but there are others. Often by this method it is impossible to determine the exact nature of prepyloric lesions whose presence is obvious. Both early cancer in this region and benign prepyloric ulcer with spasm convert the distal antrum into a narrow distorted canal, and frequently neither condition has any definite distinguishing marks. At one time hypertrophy of the pyloric muscle, which produces similar findings, often was indistinguishable from prepyloric cancer or ulcer, but the differential characteristics of pyloric hypertrophy have been learned and a roentgenologic diagnosis can be made in most cases.

Drs. Schindler and Templeton have mentioned some of the limitations of gastroscopy, *e.g.*, that in many instances there are blind spots in the stomach that cannot be inspected with the gastroscope, notably the dome of the cardia, the lesser curvature distal to the angle, and a portion of the greater curvature opposite the angle. Inspection of the duodenal bulb is an essential feature of the gastric examination and cannot be effected with the gastroscope. None of these limitations apply to the roentgen ray for it will exhibit anatomic changes in any part of the gastric or duodenal lumen.

One concession to gastroscopy I offer willingly and that is its generally recognized ability to establish or exclude the presence of chronic gastritis. Here the roentgen ray is not altogether inadequate, and some of the European roentgenologists have become proficient in making the diagnosis. Chronic gastritis of the ulcerative type is recognizable roentgenologically by its characteristic multiple small erosions, which in the face view are marked by fleck-like deposits of barium and appear in the tangential view as sharply pointed indentations in the mucosa. Lately, also, by following the dicta of my good friend, Hans Heinrich Berg, I have ventured the diagnosis of localized hypertrophic gastritis in several cases and was fortunate enough to have the diagnosis confirmed by gastroscopy in every instance. Nevertheless, I feel that the roentgenologic method has many limitations in the diagnosis of non-ulcerative chronic gastritis, that there is still much to learn in regard to technic and interpretation, and that gastroscopy should be carried out in every suspected case in order to confirm or correct the roentgenologic opinion. Further, I hope that neither the roentgenologic nor the gastroscopic diagnosis of gastritis will become common until the morbid anatomy of the disease, its right to be considered a pathologic entity, and its clinical significance become better understood and more firmly established.

It has been publicly urged that gastroscopy be applied as a routine in examination of the stomach. It seems to me that this will not be warranted until it has been shown conclusively that gastroscopy is more uniformly accurate in diagnosis than roentgenoscopy and is attended with as little risk to the patient. As is well known, in several instances the stomach has been perforated by the gastroscope and with fatal results. When medical roentgenology was new it suffered from the enthusiastic claims of its ardent practitioners and its progress was retarded. It is to be hoped that this history will not be repeated in the case of the gastroscope.

Notwithstanding all these doubts, reservations, and cautions, I am convinced that gastroscopy has already won a place as a useful adjunct in the diagnosis of gastric diseases, and if its applications can be extended with facility, safety, and substantial benefit, I shall gladly join in the general applause.

CASE REPORTS AND NEW DEVICES

PHYTOBEZOAR OF PERSIMMON ORIGIN

By FLOYD D. RODGERS, M.D., *Columbia, South Carolina*

In 1935, Dr. Harry C. Schmeisser, of Memphis, Tenn., reported[1] two cases of phytobezoar of persimmon origin, and in his search of the literature he had found 30 authentic cases of this type, his own two cases making 32. The one reported below makes 33.

Case 1. F. H., white, male, a farmer, aged 59 years, was admitted to the Veterans' Hospital for treatment of hemorrhoids. He was sent to the x-ray department for a routine gastro-intestinal examination on Nov. 9, 1935, with a history of gastro-intestinal distress. The fluoroscopic examination clearly demonstrated that there was a foreign body in the stomach. In fact, on manipulation, the observer realized that he was dealing with two foreign bodies. In the first examination, it was rather difficult to dislodge the cone-shaped body in the pyloric end of the stomach, but the larger half of the mass could be freely moved in the cardiac end. The patient was asked to return on the following morning for further investigation. On his arrival, the next day, he remarked that the manipulation had cured him, as he had had a comfortable night and felt fine.

Fig. 1. Both masses are clearly demonstrated, with a small amount of barium clinging to the phytobezoar as it does not penetrate the mass.

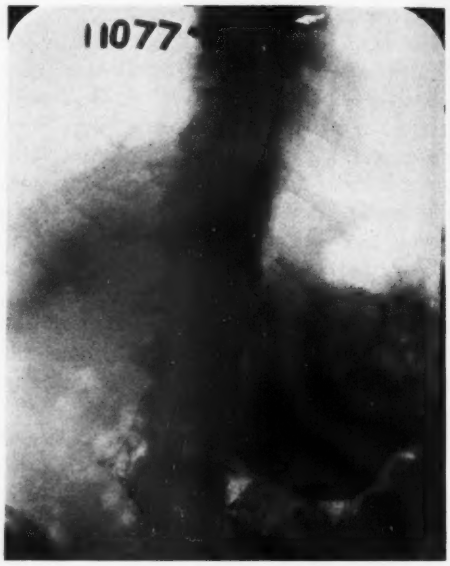


Fig. 2. Foreign bodies may be seen, with a small amount of barium in the stomach.

After the discovery of these foreign bodies, the observer immediately thought of the phytobezoar of persimmon origin and questioned the patient along this line. His story was a classic.

History.—The patient had had chronic constipation extending back over a period of at least 20 years, but had been considerably worse during the past year. He had taken cathartics, and for the past seven months it had been necessary to take a cathartic of some kind or there would be no bowel movement at all. He had a considerable accumulation of gas in the gastro-intestinal tract at times. Occasionally, he was slightly nauseated but there had been few attacks of vomiting. He had no history of epigastric pain. There had been no vomiting of blood, nor bleeding from the intestinal tract other than from the hemorrhoids for which he was admitted to the hospital. His gastro-intestinal symptoms bore no relation to meals and were not seasonal in type. He denied that he had ever been jaundiced. The patient gave no history of any edema of the

[1] South. Med. Jour., November, 1935, **28**, 987–992.

feet nor any great amount of dyspnea, although he stated that at times he had had fainting sensations, which had been ascribed to his gastro-intestinal condition.

The patient was in James Walker Hospital, Wilmington, N. C., for a period of treatment for the gastro-intestinal condition mentioned above. While there, he was put on a rather scant diet consisting of milk and cereals. He was discharged from that hospital on Sept. 7, 1935, and on the following day, being still on a very scant diet, his stomach was empty and he felt very hungry. In short, while he was out in the field where some persimmon trees grew, he ate persimmon fruit—he estimated the amount to be perhaps one and one-half pints. This was about four o'clock in the afternoon. He returned to the house and ate nothing further before retiring except some soup. Some time during the night, he became nauseated and vomited. He did not recall that there were any of the remains of the persimmons in the vomitus. He thought that he had considerable fever but his temperature was not taken. From then to the time of hospitalization he continued to have attacks of pain in the epigastrium, some nausea at times, but never vomited again.

The patient was of rather senile appearance, emaciated, and poorly nourished. His given age was 59 years; his apparent age was 70. His blood pressure 154/92; pulse, 104. Examination of the abdomen gave the impression that the liver was somewhat enlarged; however, there was also a mass in the epigastrium about the size of a medium-sized orange. This was slightly to the left of the median line and somewhat movable. Gastric analysis was made and the total acidity reported as 56; free HCl, 48; blood, negative.

Operation was performed by Dr. H. D. Coffee on Dec. 9, 1935. The stomach was greatly dilated, and there were found therein masses, firm in consistency, and about the size of a golf ball. There was an area of redness and congestion of the mucous membrane of the stomach at the pylorus. A right rectus incision was made and the stomach was exteriorized. Incision was made in the middle of the anterior surface of the stomach parallel with its long axis, and the foreign bodies were removed from it.

The post-operative condition of the patient was poor. Convalescence was rather stormy because of the extreme emaciation and dehydration. He was given saline and glucose intravenously for three days, after which a liquid diet was allowed. He gained 30 pounds in weight after the operation and was discharged from the hospital as having received maximum hospital benefit.

Upon pathological examination, the specimen removed from the stomach consisted of two black masses, irregular in shape. The surface was irregular and the ends of the masses appeared to have been broken. The total weight was 64 grams. Upon sectioning, the central portion was seen to be of a light yellow (Figs. 3 and 4), numerous seeds were present, the size of persimmon seeds. There was a mild fermentative odor present. Anatomical diagnosis was *Phytobezoar diospyri virginianæ*.

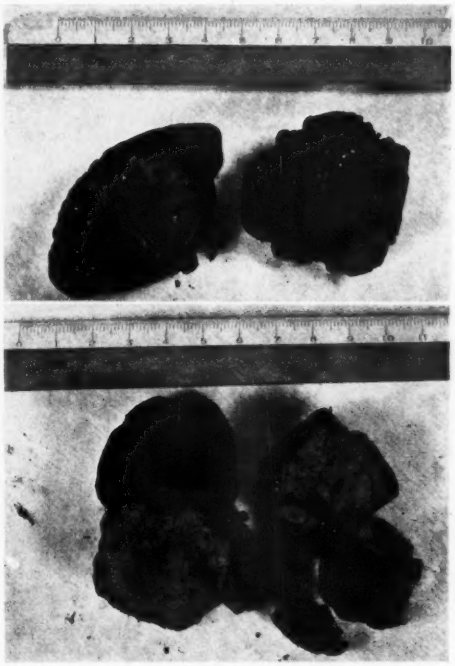


Fig. 3 (*above*). Showing the conical mass that was difficult to dislodge from the pylorus. The square mass fitted rather loosely against the conical mass.

Fig. 4 (*below*). Phytobezoar broken up, showing pulp, skins, and seed.

SUMMARY AND CONCLUSIONS

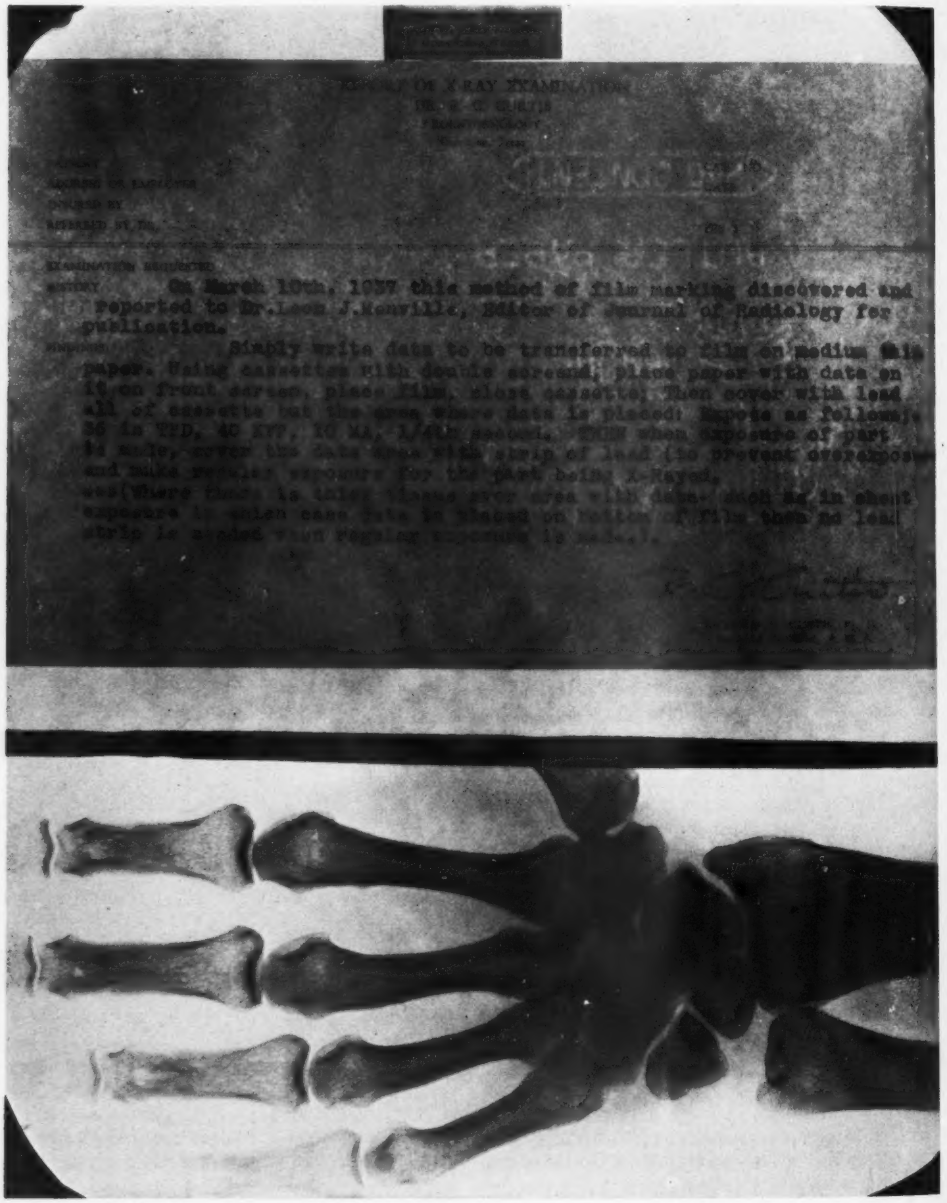
Thirty-two cases of *Phytobezoar diospyri virginianæ* have been previously collected from the American literature and one new case is reported.

The ideal conditions for the formation of phytobezoar existed in this case, *i.e.*, hunger, an empty stomach, hydrochloric acid, and persimmons.

A METHOD OF RECORDING ON FILM PERTINENT DATA RELATIVE TO PATIENT

By RICHARD C. CURTIS, M.D., *Corsicana, Texas*

To record on the film pertinent information regarding a patient, either type or write out on moderately thin paper the words and figures to be impressed on the film. Place the paper on the intensifying screen in the cassette, then place the film over the paper and close the cassette. (I use one end of the cassette for record.) Cover the cassette with a sheet of lead, leaving exposed the area under which lies the written sheet of paper, and expose as follows: 35 kv.p., 10 ma., 36 in., for one-fourth second. This makes the impression. When the exposure of the patient is made, simply



place a narrow strip of lead over the area that has been exposed for record in order to prevent over-exposure of the data strip. However, if some thick portion of tissue is over the record, the latter will not be over-exposed, even if no strip of lead is used.

In brief, this method consists of just a decrease in the intensification of the intensifying screen at the point of contact of written or printed matter. The patient's signature also may be recorded in this fashion.

This may prove a starting point for a better method of marking films, especially films which may possibly be introduced as evidence in medico-legal cases.

AN UNUSUAL CONGENITAL ANOMALY OF THE SPINE

By I. MILTON WISE, B.S., M.D., *Mobile, Alabama*

A brief discussion of the embryological development of bone is presented. This may help to explain the congenital anomaly of the spine in this case.

In the formation of the vertebræ in the embryo the mesenchyme from the sclerotomes grows mesad and comes to lie in paired masses on either side of the notochord, separated from similar masses before and behind by intersegmental arteries. In embryos of about four millimeters, each sclerotome soon differentiates into a caudal, compact portion and a less dense portion. From the former, horizontal tissue masses now grow toward the median line and enclose the notochord, thus establishing the body of each vertebra. Similarly, dorsal extensions form the vertebral arch. The looser tissue of the cranial halves also grows mesad and fills the intervals between the more dense regions. The more dense caudal half of each sclerotomic mass presently unites with the less dense cranial half of the sclerotome next caudad to form the anlages of the definitive vertebra.

Following the blastemal stage, centers of chondrification appear, two centers in the vertebral body and one in each half of the arch. These centers enlarge and fuse to form a cartilaginous vertebra. Transverse and articular processes grow out from the arch; the various ligaments arise from mesenchyme surrounding the vertebræ, and at the end of the eighth week the stage of ossification sets in. A single center appears in the body and one in each half of the arch (1).

Case Report.—S. T., white female, 39 months of age, was sent for roentgenologic examination of the spine, with a provisional diagnosis of Pott's disease. The infant had been a breech presentation at full term. Notice was taken at birth that the infant seemed to have a longer body than normal. At four months, the child sat up, and at that time a curvature was noted in the lumbar area. This seemed to grow less so that it almost disappeared. At twelve months, the child walked without difficulty. She did not limp, and fell no more often than does the average child of similar age. The mother sought advice for an increasing promi-

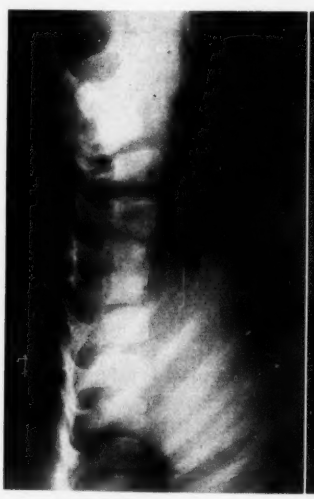


Fig. 1.

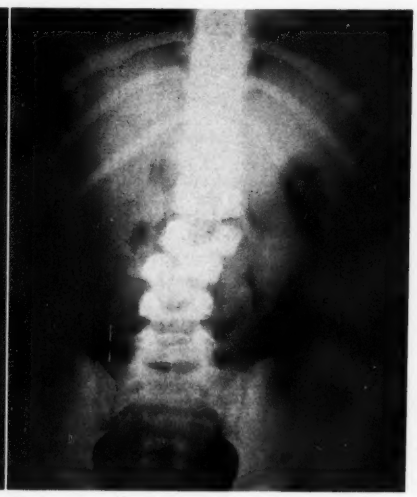


Fig. 2.

nence in the child's lumbar area which she had noted during the last several months.

Roentgenographic examination of the spine in the anteroposterior position reveals six lumbar vertebræ. The vertebral arches are not completely formed, and there exists almost a spina bifida of the fifth vertebra. The arch is closed only by a thin bony wall. Two lateral masses of bone are present on the left above and on the right below the body of the vertebra. Each mass has its own transverse process. The body of the vertebra is slightly tilted and the arch is apparently formed by the union of the center of ossification for the arch of the third vertebra on the right and the center of ossification for the arch of the fourth vertebra on the left. The centers of ossification for the arch of the third vertebra on the left and for the fourth on the right, with their transverse processes, form the unattached masses of bone. In the lateral view the bodies of the third and fourth vertebræ are fused, with a fusion, also, of the spinous processes.

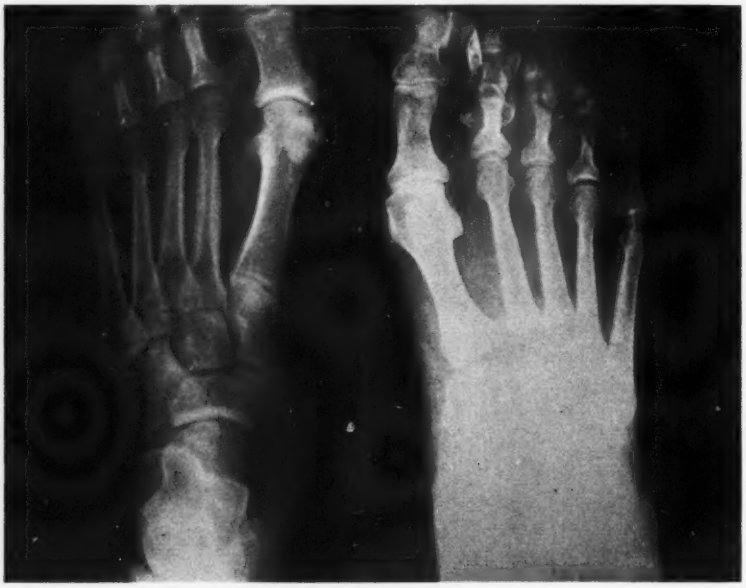


Fig. 1. An exposure made *with* the use of the wedge is shown on the *left; without* the wedge on the *right*. (*See below.*)

SUMMARY

An unusual case of congenital anomaly of the vertebral column due to atypical fusion of the centers of ossification for the vertebral arch and the presence of six lumbar vertebræ is herewith presented.

REFERENCE

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DR. CARPENTER'S ALUMINIUM WEDGE

By I. S. TROSTLER, M.D., F.A.C.R., F.A.C.P., *Chicago*

For the last five or six years I have been using a simple gadget made for me by Dr. John H. Carpenter of this city, which, because of its simplicity and adaptability should be in general use.

Ordinarily, roentgenograms of the foot in the dorso-plantar position are over-exposed in the toes and distal ends of the metatarsals if fully exposed for the tarsal bones. With the use of this gadget, the exposure of the entire foot is equal and all of the bones are equally clearly shown.

The device is simply a wedge of aluminium 3½ by 3½ inches in size. It is one-half inch thick on one side and tapers down to a feather edge at the other side. This is placed in the tube stand, near the tube, with the thick edge away from the body and toward the toes, and the exposure made as for the ankle.

It is evident that this wedge acts as a filter, equalizing the exposure, as may be seen from the accompanying illustrations.

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MEETING FALLING BETWEEN THE DATES OF OCT. 15 and NOV. 30:

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CHICAGO ROENTGEN SOCIETY. *President*, David S. Beilin, M.D., 411 Garfield Ave.; *Vice-president*, Chester J. Challenger, M.D., 3117 Logan Blvd.; *Secretary-Treasurer*, Roe J. Maier, M.D., 7752 Halsted St. Meets second Thursday of each month, September to May, except December.

ILLINOIS RADIOLOGICAL SOCIETY. *President*, Ivan Brouse, M.D., 316 W. State, Jacksonville; *Vice-president*, Cesar Gianturco, M.D., Carle Hospital Clinic, Urbana; *Secretary-Treasurer*, Edmund P. Halley, M.D., 968 Citizens Bldg., Decatur. Meetings quarterly by announcement.

ILLINOIS STATE MEDICAL SOCIETY, SECTION OF RADIOLOGY. *President*, Roswell T. Pettit, M.D., 728 Columbus St., Ottawa; *Secretary*, Ralph G. Willy, M.D., 1138 N. Leavitt St., Chicago.

INDIANA

INDIANA ROENTGEN SOCIETY. *President*, J. N. Collins, M.D., 23 E. Ohio St., Indianapolis; *President-elect*, Stanley Clark, M.D., 108 N. Main St., South Bend; *Vice-president*, Juan Rodriguez, M.D., 2903 Fairfield Ave., Fort Wayne; *Secretary-Treasurer*, Clifford C. Taylor, M.D., 23 E. Ohio St., Indianapolis. Annual meeting in May.

IOWA

THE IOWA X-RAY CLUB. Holds luncheon and business meeting during annual session of Iowa State Medical Society.

MAINE

See New England Roentgen Ray Society.

MARYLAND

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, H. E. Wright, M.D., 101 W. Read St., Baltimore. Meetings each Monday night.

MASSACHUSETTS

See New England Roentgen Ray Society.

MICHIGAN

DETROIT X-RAY AND RADIUM SOCIETY. *Presi-*

dent, C. C. Birkelo, M.D., Herman Keifer Hospital; *Vice-president*, E. W. Hall, M.D., 10 Peterboro St.; *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital. Meetings first Thursday of each month from October to May, inclusive, at Wayne County Medical Society Bldg.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *President*, J. C. Kenning, M.D., 1536 David Whitney Bldg., Detroit; *Vice-president*, A. W. Chase, M.D., 133 Toledo St., Adrian; *Secretary-Treasurer*, C. S. Davenport, M.D., 609 Carey St., Lansing.

MINNESOTA

MINNESOTA RADIOLOGICAL SOCIETY. *President*, Walter H. Ude, M.D., 78 S. 9th St., Minneapolis; *Vice-president*, Leo G. Rigler, M.D., University Hospitals, Minneapolis; *Secretary-Treasurer*, Harry Weber, M.D., 102 Second Ave., S. W., Rochester. Meetings quarterly.

MISSOURI

THE KANSAS CITY RADIOLOGICAL SOCIETY. *President*, L. G. Allen, M.D., 907 N. 7th St., Kansas City, Mo.; *Secretary*, Ira H. Lockwood, M.D., 306 E. 12th St., Kansas City, Mo. Meetings last Thursday of each month.

THE ST. LOUIS SOCIETY OF RADIOLOGISTS. *President*, Joseph C. Peden, M.D., 634 N. Grand Blvd.; *Secretary*, W. K. Mueller, M.D., 607 N. Grand Blvd. Meetings fourth Wednesday of each month.

NEBRASKA

NEBRASKA STATE RADIOLOGICAL SOCIETY. *President*, Howard B. Hunt, M.D., 4740 Hickory St., Omaha; *Secretary*, D. Arnold Dowell, M.D., 117 S. 17th St., Omaha. Meetings first Wednesday of each month at 7 P.M. in Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY

(Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut.) *President*, Frank E. Wheatley, M.D., 520 Beacon St., Boston; *Secretary*, E. C. Vogt, M.D., 300 Longwood Ave., Boston. Meetings third Friday of each month from October to May, inclusive, usually at Boston Medical Library.

NEW HAMPSHIRE

See New England Roentgen Ray Society.

NEW JERSEY

NEW JERSEY STATE RADIOLOGICAL SOCIETY. *President*, W. W. Maver, M.D., 532 Bergen Ave., Jersey City; *Vice-president*, J. D. Tidaback, M.D., 382 Springfield, Summit; *Secretary*, P. S. Avery, M.D., Middlesex General Hospital, New Brunswick. Meetings at Atlantic City at time of State Medical Society, and Midwinter in Newark as called by President.

NEW YORK

BROOKLYN ROENTGEN SOCIETY. *President*, Albert Voltz, M.D., 115–120 Myrtle Avenue, Richmond Hill; *Vice-president*, A. L. L. Bell, M.D., Long Island College Hospital, Henry, Pacific, and Amity Sts., Brooklyn; *Secretary-Treasurer*, E. Mendelson, M.D., 132 Parkside Ave., Brooklyn. Meetings first Tuesday in each month at place designated by president.

BUFFALO RADIOLOGICAL SOCIETY. *President*, John Barnes, M.D., 875 Lafayette Ave.; *Vice-president*, W. L. Mattick, M.D., 290 Highland Drive; *Secretary-Treasurer*, J. S. Gian-Franceschi, M.D., 610 Niagara Street. Meetings second Monday evening each month.

CENTRAL NEW YORK ROENTGEN-RAY SOCIETY. *President*, W. E. Achilles, M.D., 60 Seneca St., Geneva; *Vice-president*, M. T. Powers, M.D., 250 Genesee St., Utica; *Secretary-Treasurer*, Carlton F. Potter, M.D., 425 Waverly Ave., Syracuse. Meetings held in January, May, and October as called by Executive Committee.

LONG ISLAND RADIOLOGICAL SOCIETY. *President*, David E. Ehrlich, M.D., 27 W. 86th St., New York City; *Vice-president*, H. Koiransky, M.D., 43–37 47th St., Long Island; *Secretary*, S. Schenck, M.D., 115 Eastern Parkway, Brooklyn; *Treasurer*, Moses Goodman, M.D., 45–01 Skillman Ave., Long Island. Meetings third Thursday evening each month at Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *President*, E. F. Merrill, M.D., 30 W. 59th St., New York City; *Vice-president*, I. W. Lewis, M.D.; *Secretary*, H. K. Taylor, M.D., 667 Madison Ave., New York City; *Treasurer*, R. D. Duckworth, M.D., 170 Maple Ave., White Plains. Meetings third Monday evening each month at Academy of Medicine.

ROCHESTER ROENTGEN-RAY SOCIETY. *Chairman*, Joseph H. Green, M.D., 277 Alexander

St.; *Secretary*, S. C. Davidson, M.D., 277 Alexander St. Meetings at convenience of committee.

SOCIETY OF RADIOLOGICAL ECONOMICS OF NEW YORK. *President*, Albert L. Voltz, M.D., 115–120 Myrtle Ave., Richmond Hill; *Vice-president*, M. M. Pomeranz, M.D., 911 Park Ave., New York City; *Secretary*, W. F. Francis, M.D.; *Treasurer*, Theodore West, M.D., United Hospital, Port Chester. Meetings first Monday evening each month at McAlpin Hotel.

NORTH CAROLINA

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *President*, Robert P. Noble, M.D., 127 W. Hargett St., Raleigh; *Vice-president*, A. L. Daughtridge, M.D., 144 Coast Line St., Rocky Mount; *Secretary-Treasurer*, Major I. Fleming, M.D., 404 Falls Road, Rocky Mount. Meetings with State meeting in May, and meeting in October.

OHIO

CLEVELAND RADIOLOGICAL SOCIETY. *President*, North W. Shetter, M.D., Lakewood City Hospital, Lakewood; *Vice-president*, John Heberding, M.D., St. Elizabeth's Hospital, Youngstown; *Secretary-Treasurer*, Harry Hauser, M.D., Cleveland City Hospital, Cleveland. Meetings at 6:30 P.M. at Cleveland Chamber of Commerce Club on fourth Monday of each month from October to April, inclusive.

RADIOLOGICAL SOCIETY OF THE ACADEMY OF MEDICINE (Cincinnati Roentgenologists). *President*, George Benzing, M.D., St. Elizabeth Hospital, Covington, Ky.; *Secretary-Treasurer*, Justin E. McCarthy, M.D., 707 Race St., Cincinnati, Ohio. Meetings held third Tuesday of each month.

PENNSYLVANIA

PENNSYLVANIA RADIOLOGICAL SOCIETY. *President*, Sydney J. Hawley, M.D., Geisinger Memorial Hospital, Danville; *First Vice-president*, William J. McGregor, M.D., 744 Franklin Ave., Wilkinsburg; *Second Vice-president*, Oscar M. Weaver, M.D., 12 S. Main St., Lewistown; *Secretary-Treasurer*, Lloyd E. Wurster, M.D., 416 Pine St., Williamsport; *President-elect*, Charles S. Caldwell, M.D., 520 S. Aiken Ave., Pittsburgh. Annual meeting, May, 1938. Exact date and place to be decided.

PHILADELPHIA ROENTGEN RAY SOCIETY. *President*, Thomas P. Laughery, M.D., Germantown Hospital; *Vice-president*, Elwood E. Downs, M.D., Jeans Hospital, Fox Chase; *Secretary*, Barton H. Young, M.D., Temple University Hospital; *Treasurer*, R. Manges Smith, M.D., Jefferson Hospital. Meetings first Thursday of each month from October to May, Thompson Hall, College of Physicians, 19 S. 22nd St., 8:15 P.M.

RHODE ISLAND

See New England Roentgen Ray Society.

SOUTH CAROLINA

SOUTH CAROLINA X-RAY SOCIETY. *President*, Robert B. Taft, M.D., 105 Rutledge Ave., Charleston; *Secretary-Treasurer*, Hillyer Rudisill, M.D., Roper Hospital, Charleston. Meetings in Charleston on first Thursday in November, also at time and place of South Carolina State Medical Association.

SOUTH DAKOTA

Meets with Minnesota Radiological Society.

TENNESSEE

MEMPHIS ROENTGEN CLUB. Chairmanship rotates monthly in alphabetical order. Meetings second Tuesday of each month at University Center.

TENNESSEE STATE RADIOLOGICAL SOCIETY. *President*, H. S. Shoulders, M.D., 246 Doctors Bldg., Nashville; *Vice-president*, S. S. Marchbanks, M.D., 508 Medical Arts Bldg., Chattanooga; *Secretary-Treasurer*, Franklin B. Bogart, M.D., 311 Medical Arts Bldg., Chattanooga. Meeting annually with State Medical Society in April.

VERMONT

See New England Roentgen Ray Society.

VIRGINIA

RADIOLOGICAL SOCIETY OF VIRGINIA. *President*, Fred M. Hodges, M.D., 100 W. Franklin St., Richmond; *Vice-president*, L. F. Magruder, M.D., Raleigh and College Aves., Norfolk; *Secretary*, V. W. Archer, University of Virginia Hospital, Charlottesville.

WASHINGTON

WASHINGTON STATE RADIOLOGICAL SOCIETY. *President*, H. E. Nichols, M.D., Stimson Bldg., Seattle; *Secretary*, T. T. Dawson, M.D., Fourth and Pike Bldg., Seattle. Meetings fourth Monday of each month at College Club.

EDITORIAL

LEON J. MENVILLE, M.D., *Editor* HOWARD P. DOUB, M.D., *Associate Editor*

FAMILY RECORDS

Those who heard the paper on "The Relation of Heredity to the Occurrence of Cancer," read by Dr. Maud Slye at the Cincinnati meeting of the Radiological Society, and have followed her work in the last quarter of a century, are bound to be impressed with the necessity for active, practical application of the results of her observations. Reduced to its simplest possible form, Dr. Slye's theory of heredity explaining both the occurrence of malignancy and its location is that there is one unit recessive genetic factor for each type of malignancy, carcinoma, sarcoma, and leukemic disease; and that there is also one unit recessive genetic factor for each location of malignancy, such as the breast, the stomach, or the lip. The occurrence of breast cancer, for example, would therefore require two unit recessive factors, one for malignancy of the epithelium and the other for its location in the breast.

If Dr. Slye's theory is sound, she should be able to breed carcinoma, sarcoma, leukemia, or any combination of them, into families of mice, and she should be able to control the location of these diseases. Furthermore, she should also be able to prophesy as to the number of cases of these different varieties of malignant diseases and their combinations to be expected in a given number of individuals, and she should be able to state not only what the mathematical expectancy of such tumors will be, but also where they will be located. This is exactly what she has done, and her mathematical demonstrations have corresponded so exactly with the theory that it must be accepted as proved. Rarely does a scientist succeed in reaching a prime goal with such completeness, and yet we must not permit close application to the minutiæ of Dr. Slye's report to prevent us from fully appreciating the importance of her fundamentals, and the fact that this work has now assumed tremendous practical importance.

What is that practical importance? It is that we should apply to human families these findings so that we may be able ultimately to breed cancer out of the human race as she has bred it out of mouse families, for what, in terms of human life, would amount to more than 3,000 years. This could be accomplished by the same amount of attention to the mating of individuals with cancer in their families as is now paid by intelligent persons to idiopathic epilepsy.

The first essential in such a project is the keeping of adequate family records. The task of keeping such records is a slow, painstaking, rather intricate procedure, but is not beyond the abilities of any physician sufficiently industrious and intelligent to practise his profession. Briefly, such records include the following data:

1. Hereditary data.
2. Data concerning the patient.
3. Data concerning the neoplasm as an entity.
4. Data bearing on the external cause of cancer in whatever organ it may occur.

This should supply scientific data, not only on the patient himself and his heredity, but also data concerning the external causative factors in every type of malignancy. It is real scientific research which is always difficult, but always worth while. Already, several county medical societies and at least one middle-western State medical society have established bureaus for keeping such records. Should we not, as individual radiologists and also as a great scientific organization, help to accomplish this fundamental work in the control of human cancer? At the moment there must be many members of the Radiological Society who are willing to undertake the labor of this scientific research, and to use their influence in establishing state and national bureaus.

ARTHUR W. ERSKINE, M.D.

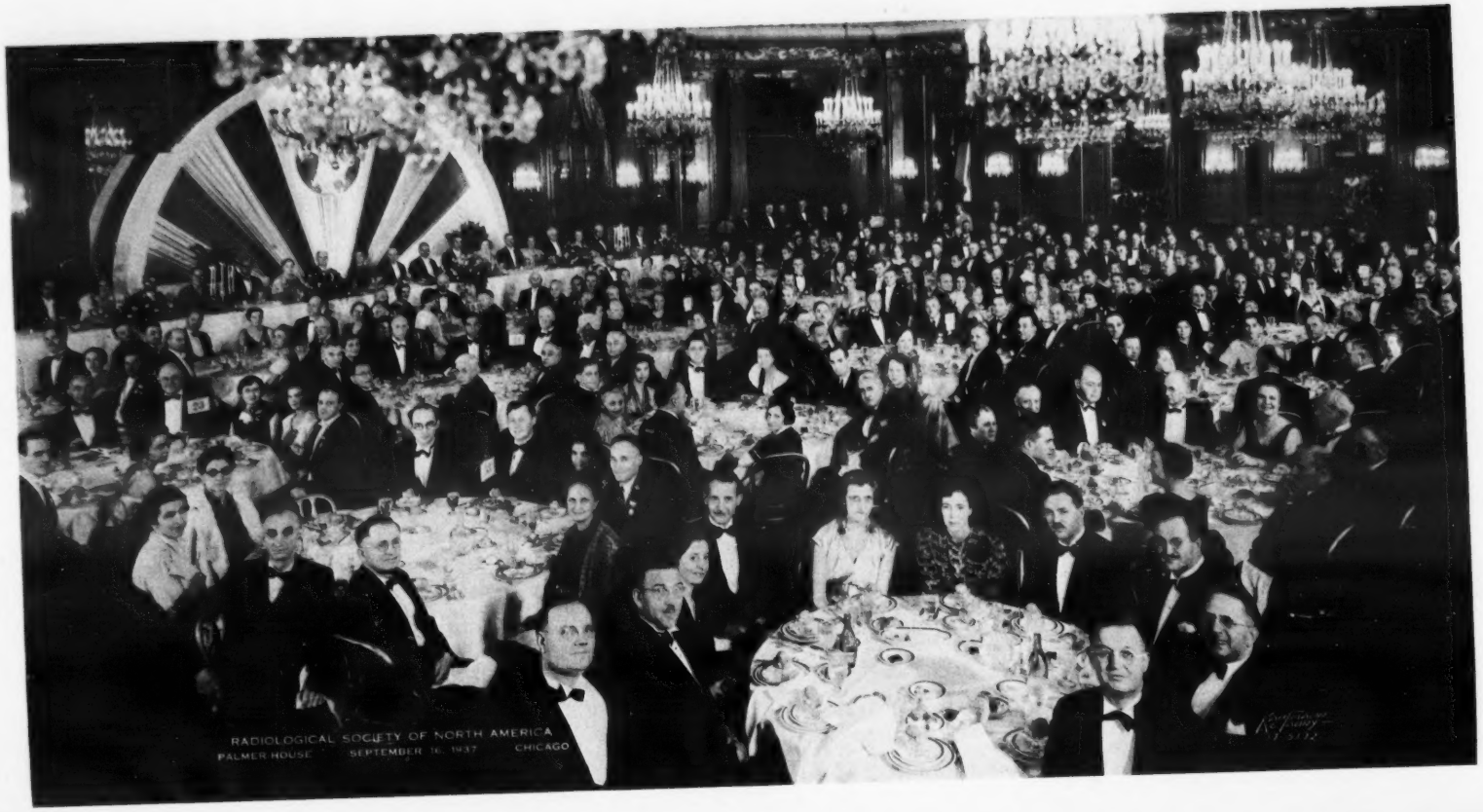
SOME PROBLEMS CONFRONTING THE RADIOLOGIST TO-DAY[1]

Within the short period of its growth no specialty of medicine has become such an indispensable part of the art of medicine as has radiology. Indeed, the science of radiology has caused such a change in the fundamentals of diagnosis and treatment relating to many branches of medicine that radiological procedures have become an indispensable prerequisite for the pursuit of many of these specialties. It is not difficult to imagine the chaotic state which would prevail in the diagnosis of orthopedic, gastro-intestinal, thoracic, and neurologic conditions if the advantages of the x-ray were suddenly made unavailable. So ramifying has the influence of this physical agent become that even the smallest hospital is now equipped with an x-ray machine and the modernization of the apparatus in many community hospitals is proudly acclaimed by the local press. With this rapid and sometimes wild development of such an important agent the problems that have arisen concerning those who would specialize in its use are quite logical ones. In addition, they are influenced somewhat by a so-called modern changing order of things that is being reflected in all parts of our community existence.

In the past radiology has been handicapped in the solution of some of its problems by the lack of any unified body that could act for, or represent with any authority, radiologists as a whole. With the formation during the past year of the Inter-Society Economics Committee, we have made a good start toward the solution of some of the problems that are continually arising regarding our work. Through the reports and bulletins of this Committee you have been apprised of the problems that confront it and what it has accomplished toward their solution. Our Society has assured this Committee of its continued support and during the past year we contributed substantially toward its financial needs. Within the last year the American Medical Association has reiterated its recognition of radiology as a specialty of medicine and emphatically concluded that it cannot be divided into professional and technical branches. Also of no little significance is the establishment by the American Hospital Association of the principles of relationships between radiologists and hospitals. How closely these will be adhered to time alone will tell, but so far a dignified and commendable approach to the solution of some of our problems has been achieved. Regardless of how much is accomplished by these means, I believe that much can and should be accomplished through education—not only through the education of others but through the education of ourselves and those who will elect to pursue radiology as a specialty. Indeed, the entire future of radiology is intimately linked with the education of those who are to follow us and it is well to recall that it is a poor teacher whose students do not excel him.

Resolutions and rules will have little effect unless we can justify our position by the quality of our work and the efficiency of the service we render. The successful radiologist strives to keep abreast of the times and to know more about his field of endeavor than his colleagues who use the x-ray only incidentally in their practice. When this prevails, he will have become such an indispensable ally of his professional colleagues or institutional staff that there should be no question about the security of his practice. A specialty that has developed such ramifying interests as radiology demands constant study and opportunities for scientific discussion. Through the medium of our annual meetings and Journal these opportunities are provided. However, I believe that we should seriously consider some means of extending them as far as our own members are concerned. The formation of the American Board of Radiology and its qualifying examination has created a demand for so-called "refresher courses," and here at this meeting of the International Congress the instructional courses are filled to capacity. I thoroughly believe that the Radiological Society of North America could offer a real service to radiology and our members by providing at our annual meeting and at such other times and places as may be deemed advisable, short, well-planned, and timely instructional or refresher courses by representative radiologists. Such courses should be limited to members of the Society and a nominal charge made to defer the cost of preparing the material involved. The arrangement of these courses could well be a function of our Educational and Publicity Committee. The value of such forms of instruction has already been established by other specialists in

[1] Presidential address delivered at the Annual Banquet of the Radiological Society of North America, Chicago, Sept. 16, 1937.


RADIOLOGICAL SOCIETY OF NORTH AMERICA
PALMER HOUSE SEPTEMBER 16, 1937 CHICAGO

medicine, notably the ophthalmologists and oto-rhinologists.

There are other ways in which the prestige of radiology may be enhanced by means of education. I refer now to a conservative educational program for the layman and fellow-practitioners concerning the usefulness of x-rays properly applied. The American Medical Association, the College of Surgeons, various State medical societies and other organizations have done much to stimulate the interest of the layman in his state of health through the means of popular articles, radio broadcasts, educational films, public meetings, etc. I believe that there is a real opportunity for our Society to do likewise in the interests of the general public and radiology.

Last year your Executive Committee investigated the cost of producing a high quality educational moving picture film that would portray to lay audiences in an ethical and conservative manner the value of radiological procedures. The expense of producing such a film proved beyond the budget of our Society and the idea was temporarily abandoned. Through such means and many others at the disposal of our Educational Committee the general public may acquire a greater appreciation of the value of x-rays as related to their own health and the practice of medicine. When the average layman learns that the proper application of x-rays is something more than the taking of a picture, his conception of a radiologist will change from that of a glorified photographer to that of a dignified specialist of medicine. In our every-day contact with patients we as radiologists can do much to enhance the prestige of our specialty. This cannot be done when patients are seen only by our technical assistants. We should not lose sight of the fact that we are consultants in medicine and a personal contact with all our patients and a sympathetic interest in their aches and pains will do much to assure them that they are paying for a physician's opinion rather than a snapshot of some part of their anatomy. The casual interest of some radiologists in their patients and the institutions which they serve is in no small way responsible for the desire in some quarters to dispense with the need of a radiologic consultant. The practice of radiology is the practice of medicine and it behooves us to conduct our work and our treatment of patients accordingly. We are not without fault in some of the problems that confront us but many of these may be overcome and the prestige of radiology increased if we will adhere to the ideals and purposes of our specialty. The effect of an educational program for ourselves, fellow-practitioners, and laymen will be infinitely more permanent and will more assuredly secure the place of the radiologist as an indispensable specialist of medicine than resolutions and agreements which are easily modified to suit the whims of those who may be in power.

JOHN D. CAMP, M.D., *President*
Rochester, Minn.

ANNOUNCEMENTS

PRESENTATION OF GOLD MEDAL AWARD TO GEORGE W. HOLMES, M.D.

By JOHN D. CAMP, M.D.

Ladies and Gentlemen: It is now my honor and privilege to present the highest award of our Society—an award that we consider the most distinguished in the field of Radiology in America—the Gold Medal of the Radiological Society of North America. We have chosen for this award one whose contributions to scientific radiology are of world-wide renown, one whose eminence in the field of education in radiology is unchallenged, and one who was a pioneer in the development of the tumor clinic as a scientific means for the study and treatment of cancer and neoplastic disease.

This Gold Medal has been awarded to a small and distinguished number of physicians and physicists, all leaders in the field of radiology during the past thirty years. It shares, by such association, in the gentle lustre shed by these great men, and with the passing years has taken on the additional distinction of being the award of the largest radiological society in the world.

Doctor George Winslow Holmes, we present to you the Gold Medal of the Radiological Society of North America.

FIFTEENTH ANNUAL MEETING OF THE ACADEMY OF PHYSICAL MEDICINE

Philadelphia, Oct. 19, 20, 21

The Fifteenth Annual Meeting of the Academy of Physical Medicine will be held at the

Hotel Walton, Philadelphia, Oct. 19, 20, 21, 1937. The Academy, which is international in scope, will present a scientific program based on reports of the most recent research and practice of the various specialties. In addition to the lectures, demonstration clinics will be held at the hospitals of the University of Pennsylvania, Jefferson Medical College, and Temple University.

A copy of the program may be had by addressing William D. McFee, M.D., Chairman, Committee on Program and Publication, 41 Bay State Road, Boston, Mass.

AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS

The first West Coast meeting of the American Academy of Orthopedic Surgeons will be held January 16–20, 1938, at the Hotel Biltmore, Los Angeles. Special trains will be run, with stop-overs at Santa Fe, the Grand Canyon, San Francisco and other points. For further information write to Robert L. Lewin, Hotel Biltmore, Los Angeles, California.

IN MEMORIAM

Stephen V. Cotter, M.D., until his death on May 30, 1937, a valued member of the Radiological Society of North America, was born in Buffalo, N. Y., on May 2, 1894. He received his pre-medical education at Canisius College, and entered the St. Louis University in 1916, receiving his degree of M.D. in 1920. Dr. Cotter served his internship in St. Mary's Hospital, St. Louis, Mo., and was licensed to practise medicine and surgery in the State of Missouri, on Jan. 21, 1920, and in New York State on July 17, 1920.

Dr. Cotter located in Lackawanna, N. Y., doing general practice. In 1921 he took up the extensive study of roentgenology, studying under men in Buffalo, New York, and Boston. At the time of his death, he was attending roentgenologist at Our Lady of Victory Hospital, Lackawanna, N. Y., and Mercy Hospital, Buffalo, N. Y. He had been on the staff of Our Lady of Victory Hospital since 1921 and of Mercy Hospital since 1928.

Dr. Cotter was a member of the American Medical Association; the Medical Society of the State of New York; Medical Society, County of Erie; the Radiological Society of North America, and the Buffalo Radiological Society.

CORRECTION

On page 736 of the June, 1937, number of RADIOLOGY, in the first line below the illustration, the chemical formula "(CS_2)" should read "(SO_2)."

I. S. TROSTLER, M.D.

BOOK REVIEW

ARCHIVOS DA FUNDACAO GAFFREE E. GUINLE By PROF. EDUARDO RABELLO, PROF. A. OZORIO de ALMEIDA, DR. GILBERTO MOURA COSTA, and DR. A. CERQUEIRA LUZ. A volume of 223 pages. Published by Rodriques & Company, Rio de Janeiro, 1937.

The first report of this paper was read before the National Academy of Medicine, June 10, 1937, and entails a theoretical and practical development of an x-ray machine by the use of which the dose of x-rays in an irradiated medium can be concentrated or dispersed at will by imparting to the x-ray tube simultaneous motion in two planes at right-angles to each other. The text is in both Portuguese and English. One awaits with interest a report on the clinical applications of this device.

ABSTRACTS OF CURRENT LITERATURE

CONTENTS BY SUBJECT

THE FOLLOWING ABSTRACTORS HAVE CONTRIBUTED TO THIS ISSUE

S. M. ATKINS, M.D., of Waterbury, Conn.
S. RICHARD BEATTY, M.D., of Madison, Wis.
J. E. HABBE, M.D., of Milwaukee, Wis.
L. G. JACOBS, M.D., of Madison, Wis.
ERNST A. POHLE, M.D., Ph.D., of Madison, Wis.
CHARLES G. SUTHERLAND, M.B. (Tor.), of Rochester, Minn.

ABSTRACTS IN THIS ISSUE LISTED ALPHABETICALLY BY AUTHORS

CANCER (DIAGNOSIS)

Heredity of Cancer. Jules Bauer. Le Cancer, 1935, **12,** 238–250.

In spite of the importance of exogenous etiologic factors, the etiology of cancer is unquestionable. This has been proven by experiments on spontaneous or grafted or artificially produced tumors of animals, by clinical experiments and by a few statistical researches on human cancer. Experiments on tumors in univitelline twins confirm this opinion.

The localization of cancer in a particular organ can be shown by the incidence of multiple cancers in one family.

Two genotypical factors form the constitutional basis of cancer, one responsible for a general tendency to produce neoplasms, the other determining the location in a particular organ. We have then a system of dihybridal heredity, two couples of allelomorphic characters. It may be deduced, therefore, that if both parents have suffered from a cancer of the same organ, then 50 or 100 per cent of their offspring will be similarly afflicted. If both have cancer but of different organs, the childrens' chances for escape are much better—the same as of those with one cancerous parent.

Exogenous factors may participate in the etiology of cancer in reinforcing or even replacing either the general constitutional factor or the localizing factor.

S. Richard Beatty, M.D.

CANCER (THERAPY)

Teleradium Therapy. E. Maier. Strahlentherapie, 1937, **58,** 593.

The author describes his apparatus for teleradium therapy consisting of one 400 mg. and one 3-gram applicator. Following a brief discussion of the physical data, he reports some of the results obtained in the treatment of cancer. Since 1931, there were 1,204 patients seen, and 840 of these were treated with the 3-gram bomb. Among those were 120 cases of carcinoma of the tongue; 66 could be observed for a period of three years. Twenty of these patients are free from symptoms. The author believes that teleradium therapy is not to be considered as competition to roentgen therapy but has its very own field of usefulness and should be applied according to definitely established indications.

Ernst A. Pohle, M.D., Ph.D.

Roentgen Therapy of Carcinoma: Protracted Fractional Daily Exposures and Exposures in Periodical Series. H. Coutard. Strahlentherapie, 1937, **58,** 537.

Following a brief discussion of the well-known principles of the fractional dose method, Coutard discusses the conception of periodicity as a possible directing factor in the roentgen therapy of cancer. A survey of his clinical material of the years 1920–1929 showed that series given from 13 to 17 days, from 24 to 29 days, and from 39 to 41 days showed the best results. The difference was high enough to be significant. He considers four principal factors of importance in the treatment of undifferentiated and differentiated types of carcinoma. For the undifferentiated type they come in the following order: (1) distribution in the tissue, (2) total dose, (3) time factor, and (4) daily dose. For the highly differentiated carcinoma they change as follows: (1) distribution of intervals between series, (2) daily dose, (3) distribution in the tissue, and (4) total dose.

Ernst A. Pohle, M.D., Ph.D.

Continuous and Discontinuous Roentgen Therapy of Cancer at Long Distances and with Low Intensities: "Superteleroentgentherapy." G. G. Palmieri. Strahlentherapie, 1937, **58,** 603.

In the author's institute two x-ray tubes have been installed on the first and third floors. On the second floor are four chambers with four beds. The distance between the targets of each tube and the beds is from 3.5 to 4 meters. Patients can be exposed continuously at these long distances with about 0.25 r/min. The average daily dose used so far amounts to 200 r given in $13^1/_2$ hours which is usually applied in three series of $4^1/_2$ hours each. The skin tolerates large doses under these conditions; epidermiolysis does not occur until 5,000 to 5,500 r have been applied. Occasionally the total doses reached 8,000 r without serious effects. The author promised to report his results at the Fifth International Congress in Chicago.

Ernst A. Pohle, M.D., Ph.D.

THE COLON

Attack of Partial Occlusion Due to Diverticulitis in a Case with Diverticulosis of the Colon and Diverticulitis of the Sigmoid. Gondard and Blanc. Bull. et Mém. Soc. Radiol. Méd. de France, February, 1937, **25,** 28, 29.

A patient who had suffered an attack of acute abdominal pain, with evidence of partial obstruction and a mass in the pelvis, was demonstrated to have numerous diverticula of the colon associated, in the sigmoid, with an irregular constriction.

S. Richard Beatty, M.D.

CONTRAST MEDIA

The Barium Enema in Intestinal Intussusception of Children. P. Lamarque and P. Betoulieres. Bull. et Mém. Soc. Radiol. Méd. de France, January, 1937, **25,** 29–31.

The authors believe the barium enema with fluoroscopic and radiographic observation to be very useful in the diagnosis of intestinal intussusception in children, and in locating the site prior to laparotomy. They have used never more than one meter of pressure and have had no accidents.

The barium enema makes possible an early and more certain diagnosis. The picture is characteristic in intussusception of the colon or ilio-colic intussusception. The enema is useless in lesions higher, except in excluding these types.

The therapeutic results of reducing the intussusception have not been observed in the six cases reported, as all were subjected to surgery. Unquestionably the use of the barium enema has resulted in a much lower mortality.

S. RICHARD BEATTY, M.D.

THE CRANIUM

Roentgen Signs in Hydrocephalus and Their Diagnostic Value. M. B. Kopylov. Am. Jour. Roentgenol. and Rad. Ther., November, 1936, **36,** 659–673.

The variations in the skull changes in this condition can be explained by consideration of the physiological factors, the peculiarities due to age, the type of skull and its parts, and the part played by hydrodynamics. Thus an open hydrocephalus with fluid in the subarachnoid must produce changes different from the closed, in which the subarachnoid spaces are dry and the convolutions of the brain can press directly on the bones. In like manner other changes found can be explained.

The principal roentgen signs in the open are as follows: Sella turcica in children shows no change but in adult at later stages becomes cup-shaped, the sutures often distended and in children the dentations at the sutures elongated. The child's skull is smooth and round or spherical with increased radius of vault and fossæ.

In the closed type the changes in the sella turcica depend on whether the closure is of the upper (region of sylvian aqueduct), or lower type (region of fourth ventricle). In the lower, the posterior clinoid process inclines anteriorly, the dorsum is atrophied, shortened, or bent anteriorly, the entrance is widened very slightly, and the floor is deepened chiefly in the back part. In the upper, the posterior clinoid process and the dorsum become straightened and inclined posteriorly. The anterior aspect of the dorsum is atrophied. Entrance is more extended and the floor more evenly deepened than in the lower.

In both types of the closed, the digital impressions and vessel grooves are deepened, the sutures are often distended but the general skull configuration is not definitely abnormal.

S. M. ATKINS, M.D.

EPILATION OF SCALP

The Depth Dose during Epilation of the Scalp by Irradiation. A. Proppe. Strahlentherapie, 1937, **59,** 139.

The author determined the dose reaching the brain during irradiation of the scalp for epilation. A small ionization chamber was inserted in a skull after it had been filled with paraffin. Roentgen rays produced at 85 kv. and filtered through 0, 0.5, 1, and 2 mm. Al, respectively, were used. If four fields are applied, a dose of 70 per cent of the surface dose reaches the brain substance in the depth. For an epilation dose effective in the skin of 400 r, this amounts to 280 r within the brain. If five and six fields are used, this dose increases materially, of course. The author concludes from his studies that not more than four fields should be used for epilation of the scalp, preferably according to the technic described by Schreus.

ERNST A. POHLE, M.D., Ph.D.

GALL BLADDER (NORMAL AND PATHOLOGIC)

Interpretation of Roentgen Films in Gall-bladder Diseases. Hermann Durst. München. med. Wchnschr., June 11, 1937, **84,** 932–934.

The author states that there is always more or less error in the diagnosis of gall-bladder films, there being poor correlation between the roentgen and operative findings. He therefore undertakes a comparison of these findings in his own cases which have been operated upon.

In 52 cases of stone, 27 were diagnosed by x-ray, the gall bladder being visualized; six cases showed no emptying of the gall bladder.

In 12 cases of chronic inflammation, six showed visualization with non-emptying; four no visualization.

Of all these, 52 in the first group showed colic, while all but two in the second did not. The latter group showed other symptoms as well. While there is some uncertainty about the use of colic as a sole criterion for operative intervention, careful history will usually distinguish stone from other colic. The various combinations of roentgen findings and colic are considered to have different meanings, which are set out in a tabulation.

The author considers the oral method unreliable, and uses only intravenous administration. False emptying may be caused by egg yolk given the night of administration or by the injection of hypophysin.

(Abstractor's note: The opinions of the author contrast so violently with the findings of workers in the United States, especially at the Mayo Clinic, that one would question them. The evidence given for them seems very inadequate.)

LEWIS G. JACOBS, M.D.

GASTRO-INTESTINAL TRACT (DIAGNOSIS)

Radiologic Studies of Diverticula of the Digestive Tract below the Diaphragm. J. Baumel and J. Balmes. Bull. et Mém. Soc. de Radiol. Méd. de France, January, 1937, **25,** 31–44.

Briefly reviewing the pathologic anatomy, etiology and localization of diverticula of the intestinal tract

below the diaphragm, the authors stress the necessity of careful roentgenologic technic in the attempt to demonstrate these conditions.

The technic used should be adapted to that portion of the gastro-intestinal tract in which the diverticula are sought. In the stomach, examination with a small meal from several angles, including the Trendelenburg position, is essential. Frequently the introduction of barium into the duodenum through an Einhorn tube is of value, in that the shadow of the filled stomach is avoided.

Barium or one of the flocculent solutions by mouth, followed by frequent fluoroscopy or roentgenography, is the method of examination for the small bowel.

In the case of the large intestine, three opaque meals at 20, 40, and 8 hours before roentgenography, may be used. Enemas of barium or of flocculent material, with small amounts of solution, or with complete filling and films taken before and after evacuation and after insufflation of air, are perhaps more useful in the study of the large intestine.

The details of technic, the diagnosis and the differential diagnosis of diverticulosis and diverticulitis, are discussed in detail.

S. RICHARD BEATTY, M.D.

MYOSITIS OSSIFICANS

Myositis Ossificans. C. Artus-Christiani. Lyon Chir., January–February, 1937, **34,** 5–19. (Reprinted by permission from British Med. Jour., April 10, 1937, p. 57 of Epitome of Current Medical Literature.)

The author discusses the history and pathology of myositis ossificans and describes two personal cases of the disease. Traumatic myositis ossificans is an intramuscular bony formation which appears some time after the original injury. The trauma may be an external injury, a fracture or dislocation, or a sudden muscular contraction. On the other hand, slight repeated traumas may give rise to the disease in the thigh in cavalry soldiers, and in the biceps or in the muscles of the arm or shoulder following excessive exercise of these upper arm muscles. Ossification never arises in the muscles of the hand. It is most often seen in young persons of the male sex. The thickening of the muscle usually occurs soon after the swelling caused by the injury, and may be overlooked unless there is limitation of movement or pain or an x-ray film is taken. The growth may be joined to the bone by fibrous tissue or may be isolated in the muscle. It may vary in size from the thickness of the thumb to 20 cm.

The first case described was in a man 66 years of age who, in falling, had fractured the right femur. The leg was put in extension and immobilized for three weeks. As a radiograph then showed that consolidation had not taken place and as reduction was not possible owing to a muscular growth, operation was carried out. This showed a hematoma with myositis ossificans extending into the vastus and adductor muscles. Osteosynthesis was performed, but the patient died two days later from paralytic ileus, shock, and uremia. In the second case the tumor appeared in a man 23 years of age following a kick on the thigh from a horse. The growth increased in size until, at the end of three months, the knee function was affected. Operation was carried out and the tumor, which was of bony consistency, was successfully removed.

PEPTIC ULCER

"Niche en Plateau" Due to Ulcer. A. Lacroix and A. Blondeau. Bull. et Mém. Soc. Radiol. Méd. de France, February, 1937, **25,** 158–162.

The large, flat-based niche is usually regarded as pathognomonic of gastric carcinoma. The authors present a case demonstrating an exception. A typical "niche en plateau" in an old woman, with symptoms suggesting malignancy, was observed radiologically to show marked decrease in size after three weeks' ulcer treatment and complete healing in six weeks. Such niches require a period of observation under strict treatment before a definite diagnosis can be made.

S. RICHARD BEATTY, M.D.

The Radiologic Differences in the Course of Gastric and Duodenal Ulcer. R. A. Gutmann, Parturier-Lannegrace, and Piquet. Arch. d. mal. de l'app. digestif, March, 1937, **27,** 324–326.

An important difference between gastric ulcer and duodenal ulcer is that, while the latter heals often with scarring and deformity, the former does not; consequently, it is sometimes impossible to state whether a lesion in the bulb is active or inactive. The presence of a niche in the stomach denotes activity.

S. RICHARD BEATTY, M.D.

PHLEBITIS

The Roentgen Irradiation of Acute, of Sub-acute, and of Chronic Phlebitis and Thrombophlebitis. C. Henschen and F. Becker. Schweiz. med. Wchnschr., May 15, 1937, **67,** 438–441.

The authors reviewed some literature on the irradiation of acute, sub-acute, and chronic phlebitis and thrombophlebitis, but found surprisingly little material published. A series of their own cases is reported, rather small in number. However, they are encouraged by it to the further use of the method. Good results are reported in the literature in the regression of papilledema from venous thromboses of various sorts. The authors then describe the findings in phlebitis, and state that proper treatment initiates a prompt clearing of the pathologic process. Epidemics of phlebitis differ among themselves, some showing a seasonal epidemic form in which all cases of operation may be infected. This form sometimes leads to a chronic recurring type of long duration.

In the treatment of the different forms of phlebitis there are a great many methods. Applications of alcohol, of aluminum acetate, lead water, etc., icthyol compresses, camphorated ointment of 10 per cent methyl silicate, intravenous injections of argyrol, immobilization, bandaging, galvanization, thermal treatment, diathermy and the use of massage, diet, either salt-free or low calorie, urotropin by mouth or intravenously, theobromine, witch-hazel, injection of 10 c.c. of 1 per cent novocaine in the lumbar sac, high frequency current, ultra-violet or infra-red rays, surgical excision, removal of the clot and subsequent suture, fixation abscess, protein shock, anti-streptococcic serum, polyvalent vaccine, etc., may be used.

The rule is stated that the control of epidemic cases should be through the seeking out through a possible isolation of occasional cases and the search for a vaccine against phlebitis. The action of the rays is considered to be due to a number of interlocking effects. These are both local and general, and are given in very considerable detail. These effects are mostly accompanied by citations to the authors, no original work having been done along these lines. Among the more outstanding clinical effects are the shortening of the course of the disease. The authors believe that roentgen therapy is indicated not only in the superficial structures but also in those of the deeper structures such as the pelvis, mesentery, and the skull. Concerning technic, they believe that the more acute the infection the weaker the irradiation. The basic dose lies between 100 and 200 roentgens, the actual dose given, however, is varied each time according to the condition of the patient. The irradiated area should in all cases cover the entire inflamed area.

L. G. JACOBS, M.D.

PLANIGRAPHY

Planigraphy. I.—Introduction and History. J. Robert Andrews. Am. Jour. Roentgenol. and Rad. Ther., November, 1936, **36**, 575–587.

Planigraphy is a method of roentgenographic projection of plane sections of solid objects and is effected by moving the film and roentgen tube in opposite directions simultaneously in a constant ratio by means of a connecting system which rotates about an axis that lies in the plane of the section to be projected.

The principle of body section was first described by Bocage, of France, in 1921, and since then other methods have been described by other authors, notably Kieffer, of Norwich, Conn., who discovered this principle independently in 1929. Grossmann's apparatus, now manufactured in Germany, goes under the name "Tomography."

Chaoul claims that pulmonary vessels, their divisions, the bronchi and their related pathological conditions, cavities, and spread of lung disease, can be demonstrated more clearly in this manner than by any other method.

S. M. ATKINS, M.D.

Note on Pulmonary Planigraphy. Delherm, Jacques Bernard, and Nguyen-Dinh-Hoang. Bull. et. Mém. Soc. Radiol. Méd. de France, 1937, **25**, 123–125.

It is somewhat early to make definite statements as to the relative value of planigraphy. Certainly the major reliance in study of the lung must be placed in conventional radiography and stereo-radiography. Planigraphy furnishes a method of analysis of complex images. Frequently the interpretation is difficult. Their value as an aid in diagnosis is unquestioned as it has been possible to better define such lesions as cavities and even to demonstrate cavities hidden in the usual roentgenogram by extraneous opacities.

S. RICHARD BEATTY, M.D.

PNEUMONIA

Lobar Pneumonia in Childhood. S. L. Ellenberg and A. T. Martin. New York St. Jour. Med., Jan. 15, 1937, **37**, 119–127. (Reprinted by permission from British Med. Jour., April 10, 1937, p. 59 of Epitome of Current Medical Literature.)

The authors record a clinical survey, covering five and one-half years, of 459 cases of lobar pneumonia in childhood. Of these cases, 50 per cent arose in children under the age of four years and only a few in the later ages of ten and upwards. The peak incidence was reached in the first years of life. The greatest number of cases were recorded during the late winter months of March and April, while the fewest cases arose in July. The mortality in this series was 8.6 per cent, and this could have been reduced still further by an earlier admission to hospital, as many children were sent in as a last resource. This mortality rate compares favorably with the records of other writers. The fact that the mortality is higher in children two years of age and under is also borne out by this study, for the mortality in this age group is 24 per cent as compared with a mortality of 2.1 per cent in the age group above two years. X-ray examination was useful and confirmed the diagnosis of lobar pneumonia in most cases. Meningeal irritation was noted in 24 cases and lumbar puncture showed increased pressure but no excess of cells and no organisms. The five most frequent complications were otitis media, empyema, meningismus, furunculosis, and abscesses. Empyema was the most serious complication and the one most likely to influence the course of the illness. Treatment consisted in the main in leaving the patient alone, and in good nursing. Abdominal distention needed to be carefully watched and treated with enemas at once. Oxygen is considered to be a very definite adjunct to the treatment of pneumonia, and should be used whenever cyanosis, excessive restlessness, or severe toxemia is present. The old method of giving oxygen by the open method or through a nasal catheter is condemned as being of no value. The oxygen tent only was used and proved of much value.

PNEUMOTHORAX

Spontaneous Pneumothorax from Pulmonary Metastasis of an Osteosarcoma. M. J. De Barrin. Bull. et Mém. Soc. Radiol. Méd. de France, January, 1937, **25**, 73–76.

A year after primary irradiation of an osteosarcoma of the pubic bone and during the course of a second series for local recurrence, a patient developed clinical evidence of pneumothorax. The chest film showed complete pneumothorax on the left, with fluid in the sulcus and large metastatic nodules in the other lung. Two months later films showed persistence of the pneumothorax, with absorption of the fluid. The patient died 18 months after diagnosis of the lesion. Presumably the pneumothorax was the result of rupture of the pleura by a small metastatic nodule.

S. Richard Beatty, M.D.

RADIATION INJURIES

Dangers of Introduction of Radio-active Substances into the Body. S. Laborde. Presse méd., Nov. 25, 1936, pp. 1915–1918. (Reprinted by permission from British Med. Jour., Jan. 30, 1937, p. 19 of Epitome of Current Medical Literature.)

The author warns against too high dosage in oral or other administration of radio-active substances. In general the quantities should not be in excess of those which are ingested in naturally radio-active springs, and it should be remembered that short-lived radio-active substances such as mesothorium and thorium-X are at least as dangerous as the others. It is a matter of surprise that repeated doses of from 50 to 300 micrograms of thorium-X such as are sometimes injected in treatment of painful articular affections are not more often followed by toxic effects. These may be lethal and include acute enteritis, hematemesis, necrosis of the jaw, leukemia, grave anemia, and local radiodermatitis coming on from one month to nine years after treatment; they are less frequent than among professional workers with radio-active substances, but are nevertheless to be feared, especially in those with idiosyncrasy.

Diseases Caused by X-rays and Radio-active Substances. S. Laborde and J. Leclercq. Écho méd. du Nord, Nov. 8, 1936, **6**, 797. (Reprinted by permission from British Med. Jour., Jan. 31, 1937, p. 19 of Epitome of Current Medical Literature.)

The authors give details of those diseases which are caused by x-rays or radio-active substances and which are considered to be occupational as they occur during medical or commercial work. The laws of compensation vary in the different countries, and particulars are given which show the diseases and occupations entitling the worker to compensation in France. The first of these diseases is radiodermatitis, which is easy to diagnose and is seen chiefly in workers who come in contact with tar or paraffin. Skin cancer may develop later in these cases. Cancer of the lung occurs in miners who extract pitchblende, but as there are no mines in France where radio-active substances are found, this is not in the list of compensatory diseases. Various conditions of the blood, such as anemia with leukopenia, pernicious anemia, and leukemia, are caused by x-rays, and these are included in the list. Sterility and complications of pregnancy cannot be proved to be due to these causes as there may be other factors present, and these disorders are not yet included in France. On the other hand necrosis of bone, particularly of the jaws, can be shown to be the result of work with radio-active products which entails putting these substances in the mouth. Details of the rules which govern compensation are given and the question of protection is discussed.

Recommendations suggested include working for not more than seven hours a day for five days a week, with at least one month's holiday a year. Those persons who work in the x-ray department should be particularly healthy and should have no other hospital work. For protection, the operator should be as far as possible from the x-ray apparatus and should never be exposed to direct rays. The x-ray tube should be protected by a lead screen. The worker who extracts radio-active substances should be given adequate protection. Protection against the beta-ray is easy and only necessitates handling the preparations with wooden pincers. Against the gamma-ray, protection must be by means of a lead screen, but is of necessity so difficult that the number of persons dealing with this type of ray should be as numerous as possible, so that the time spent in contact should be shortened in each individual case.

Late Injuries Due to Radiation and Appearing Following Trauma. W. Schloss. Strahlentherapie, 1937, **58**, 697.

The author has studied the relation between trauma and late injuries in previously irradiated tissue. He briefly reports five cases illustrative of this group. In one patient the trauma was of a mechanical nature; in another case it occurred because of additional radiation due to a mistaken diagnosis of recurrence, and in another case mechanical and pharmacotoxic trauma were combined. He emphasizes the necessity of drawing the attention of our patients to the possibility that injuries after irradiation may develop even years following the exposure and that irradiated tissue should be protected from all irritation.

Ernst A. Pohle, M.D., Ph.D.

RADIUM

Early Experiences with Radium. Curtis F. Burnam. Am. Jour. Roentgenol. and Rad. Ther., October, 1936, **36**, 437–452.

This article, the Janeway Memorial Lecture, in a reminiscing way, tells of the author's experiences in

procuring and applying radium in Baltimore during the years of 1911–1916, and of the acquaintances and friendships developed with others similarly engaged in studying the field of usefulness of radium in its several forms. The development of experimental and clinical knowledge of radium therapeutics is traced and some of the results obtained in those years briefly reviewed.

J. E. HABBE, M.D.

The Production of Mutations by Beta Rays of Radium in the Fruit Fly. K. G. Zimmer, H. D. Griffith, and N. W. Timofeeff-Ressovsky. Strahlentherapie, 1937, **59**, 130.

The authors describe in detail their experimental procedure for the production of mutations in the fruit fly by means of beta rays of radium. A special ionization instrument was constructed which permitted the determination of the doses applied in r. The rates of mutations were directly proportional to the dose and were identical to those produced by equivalent doses of roentgen and gamma rays. In a graph the authors plot the mutation rate and the dose in r for beta rays, Grenz rays, roentgen rays, and gamma rays—there exists linear relation.

ERNST A. POHLE, M.D., Ph.D.

Radium Therapy of Uterine Fibroids. R. Gaudu-cheau. Jour. Radiol. Electrol., January, 1937, pp. 1–4. (Reprinted by permission from the British Med. Jour., May 8, 1937, p. 75 of Epitome of Current Medical Literature.)

The author considers x-ray therapy to be the treatment of choice of uterine fibroids. However, in a limited number of cases it may be advantageous to use radium therapy instead. Radium therapy is indicated in cases in which transportation of the patient presents difficulties, or in which patients are very anxious to get through the treatment in the shortest possible time. The results of such therapy are probably just as good as those of x-ray therapy, but radium therapy presents certain dangers, such as septic uterine complications, phlebitis, and pelvic peritonitis. The author had one fatal complication among 29 cases treated with radium, but over a number of years no complications have followed x-ray therapy.

Studies of the Radiation Intensity around Radium Applicators by Means of Ionization Chambers with Thin Walls. H. Smereker. Strahlentherapie, 1937, **58**, 267.

The author describes a cylindrical ionization chamber made of aluminum 0.01 mm. thick which permits ionization measurements close to radium applicators by practically avoiding the wall effect. The results of her experiments in air are described, with special consideration of the influence of size and thickness of filter as well as the distance. Comparing the results of her measurements with those obtained by means of an ionization chamber with thick air walls, differences as high as from 60 to 70 per cent were found. With her chamber the author determined the equivalent of 1 mg.-hr. at 1 cm. distance with 0.5 mm. Pt filter at 7.74 r. She also discusses the experimental determination of Eve's constant (this constant is the number of ion pairs produced in 1 c.c. of air per second by gamma rays from radium C in equilibrium with 1 gram of radium provided there is a point source of radiation at 1 cm. distance). She states that the inverse square law cannot be used in calculating Eve's constant.

ERNST A. POHLE, M.D., Ph.D.

Limitations of Radium Therapy in Cancer of the Cervix. Palmer Findley. Am. Jour. Roentgenol. and Rad. Ther., October, 1936, **36**, 457–460.

The author, a gynecologist, states that radium is used in preference to surgery in about 10 per cent of all of his gynecological cases, about 25 per cent of all uterine fibroids, 100 per cent of all so-called essential hemorrhages from the uterus not responding to medical measures, and 100 per cent of all cervical cancers being treated by this method. In the field of malignancies he has found only about 25 per cent five-year cures for cervical cancer, which fact prompts him to urge the widespread removal of pre-cancerous lesions of the cervix by trachelorrhaphy, amputation, and cauterization.

In considering the five- and ten-year end-results in therapy of the uterine cervix, the difficulties in accurately grouping cases according to extent of involvement when first seen, is emphasized. It is also impossible to predetermine which patients will react hypersensitively to treatment, and which sluggishly. The undernourished, anemic individual, particularly if harboring infection, must be treated with caution and the debilitating factors eliminated whenever possible. Radium should be promptly removed at any sharp rise in temperature. The application of the x-ray pelvic cycle will go far in preparing the field for radium. In cases of cancer of the uterine cervix occurring in the pre-menopausal group it is important by one means or another to exclude pregnancy before starting irradiation therapy. If pregnancy is found it should, of course, be interrupted and at least a week of time allowed to elapse before starting irradiation.

J. E. HABBE, M.D.

Radiation Therapy of Skin Cancer with Special Consideration of the Radium Technic. R. Müller. Strahlentherapie, 1937, **59**, 45.

The author discusses the use of x-rays and radium in the treatment of advanced carcinoma of the skin. He prepares special radium molds filtered through 0.1 mm. Au containing from 3 to 3.5 mc. per sq. cm. of surface, which are applied for a period of seven days. Some large tumors are taken off with the endotherm knife and radium is then applied to the base. For large lesions applicators are prepared consisting of screens 1.4 cm. long and 0.4 cm. thick filtered through 1.2 mm. Pt. Instructions for arranging these screens at various

distances from the skin are given. Some lesions respond well to roentgen therapy (180 kv., 0.5 mm. Cu, 23 cm. F.S.D., 7 x 600 r applied every other day). The Coutard method does not seem to give very satisfactory results in carcinoma of the skin.

ERNST A. POHLE, M.D., Ph.D.

Qualifications for the Practice of Radium Therapy. G. W. Grier. Am. Jour. Roentgenol. and Rad. Ther., October, 1936, **36,** 453–460.

There is a similarity between the specialties of radium therapy and surgery in that in each, a specific form of treatment (radium in one instance and the knife in the other) is used in all cases actively handled by the practitioner. However, in the case of surgery, it is now well recognized by the medical profession and the public alike that adequate post-graduate instruction is essential, but in the case of radium therapy there is little recognition as yet of the importance of similar special training.

There are to-day three classes of practitioners who have a legitimate right to use radium. These are: (1) the radium specialist who confines his practice to the use of radium; (2) the radiologist who applies radium as an adjunct to the x-ray, and (3) the several clinical specialists who, in treating certain diseases belonging naturally to their specialties, must include radium applications if they are to treat certain cases most effectively.

It is probable that with improved standards of post-graduate instruction being demanded by all the special examining boards, the extended period of post-graduate instruction will permit of adequate teaching of radium therapy. However, since the Council on Medical Education and Hospitals has classified radium therapy as a branch of radiology, it would seem proper that the therapeutic radiologist should also be competent and experienced in radium therapy.

J. E. HABBE, M.D.

Radio-active Emanation Therapy in Orselina. H. Bodmer. Schweiz. med. Wchnschr., May 8, 1937, **67,** 408–410.

The paper discusses the natural emanation of the region near Orselina, in the region of Upper Lake of Locarno. The region is built up of crystallized rock, especially a mica-bearing paragneiss, characterized by a pegmatite form. Among the pegmatites are inclusions of granite extending easterly. In the mica-bearing rock there can be microscopically demonstrated with low magnification small radio-active particles of uranium-radium and of thorium-thorium C. This renders the neighboring waters radio-active. The radio-active content of the water is from 18 to 30 Maché units per liter. These waters have been used for bathing for years. The radon content of the free air varies between one and three Maché units per liter. In the treatment chamber the basal air carries in the neighborhood of five or over Maché units per liter. With regard to therapeutic use the author feels that this type of therapy has been unduly discredited by quackery and by the dangers to the blood-forming organs in the past, but that now the time has come to publish again concerning intelligent use under adequate control. The author distinguishes between weak therapy with naturally occurring emanation and strong therapy with artificially prepared emanation. The former produces reversible functional changes in the cell; the latter irreversible changes. The actual use of the latter is purely empirical, experiments being insufficient to give any reasonable basis for its employment. The treatment is used in sub-acute or chronic rheumatism or rheumatoid arthritis, or sub-acute and chronic muscular rheumatism, myalgia, neuralgia, and neuritis, gout, hypertonic states, a considerable number of skin diseases, roentgen ulcer, and certain diseases of the adnexa.

The therapy takes the form of baths with radio-active water of about 50,000 Maché units in 200 liters of water; of ingestion of 10,000 Maché units in 50 g. of water; of inhalations in the "Emanatorium" of air usually containing 5 Maché units per liter, or in the application of finely pulverized clay in oil. Very great individualization of dosage is required. There is usually a general and local reaction, consisting of slight vertigo, a tired feeling, physical and psychic unrest, sleeplessness, and increased pain in the arthritic joints. In gout a larger dose usually brings about relief of pain. In addition to the radiation in such cases, an optimum general environment is required. Orselina has the advantage of optimum all-round climate near a good source of radio-active emanation.

L. G. JACOBS, M.D.

ROENTGEN SICKNESS

Radiation Sickness: Its Possible Cause and Prevention. Harry F. Friedman and Philip Drinker. Am. Jour. Roentgenol. and Rad. Ther., October, 1936, **36,** 503–509.

The authors report the results of control of radiation sickness by means of a mask which accomplishes deionization of the air which the patient breathes while in the treatment room. It was shown by experiments by Dessauer that individuals kept in a room of high concentration of positive ions would develop symptoms similar to radiation sickness. Experimental work was next carried out by Yaglou and one of the authors (P. D.) to determine the concentration of positive and negative ions six feet from an operating roentgen tube. From laboratory experiments it was next shown that the ion content in the therapy room was vastly in excess of the normal. These experiments suggested that roentgen sickness is the result of the combined effect of some extraneous factor breathed in by the patient plus the tissue changes effected by the x-rays. It appeared that either factor alone without the other would not produce true roentgen sickness in the usual therapeutic doses.

Twenty-four patients who were receiving high voltage x-ray therapy in protracted manner upon utilizing the deionizing mask perfected by the authors were relieved of roentgen sickness in 92 per cent of the cases.

The deionizing agent in the cartridge of the mask may be either charcoal or a wire cloth of very fine mesh.

J. E. HABBE, M.D.

THE SINUSES

Accessory Nasal Sinusitis in Childhood, with Record of Bacteriological Examinations. J. Crooks and A. G. Signy. Arch. Dis. Childhood, December, 1936, **11**, 281–306. (Reprinted by permission from British Med. Jour., April 10, 1937, p. 58 of Epitome of Current Medical Literature.)

The authors state that in view of the prevalence of infection of the nose, throat, and ears in childhood it is reasonable to suppose that disease of the nasal sinuses is common in early life. One hundred instances of nasal sinusitis are recorded and analyzed. Any or all of the accessory air sinuses may be diseased in childhood, for these are all present in early life. The development of the sinuses and the scheme of investigation are described. The presence of inflammatory exudate in an air sinus is proved by aspirating fluid from the cavity and not by washing it out of the nose with a cannula in the sinus. Reasons which led to a decision to aspirate the antra in a series of children undergoing removal of tonsils and adenoids were that they had chronic respiratory complaints and that the antra could be easily punctured while under the anesthetic. Only children who had a chronic infection of the upper air passages were subjected to this procedure. The technic of the puncture and the bacteriological examination of the antra are described. The main fact that emerges is that out of 100 children having a tonsil and adenoid operation 24 were found to have mucus, mucopus, or pus in one or both antra. Most of these cases cleared up with antral lavage. In children the nose is small and easily blocked and adenoids are frequent. The common conditions giving rise to sinusitis are colds, influenza, and infectious diseases, particularly whooping-cough. Bathing in infected water is another frequent cause. Sinusitis is more common in those climates where upper respiratory infections are prevalent, and is common in children who are in chronic ill-health. X-ray examination is a valuable aid in diagnosis, and cases can be followed up by repeated examinations of this nature. A complete cure can be anticipated in most cases in several months.

SKIN DISEASES

Investigations as to the Significance of the Sulfhydrate Group for the Biologic Effects of Light. P. Wels and M. Jokisch. Strahlentherapie, 1937, **58**, 1.

The authors undertook some extensive experiments in order to discover a relationship between the biologic effects of light and chemical reactions. If an albumin solution is exposed to a quartz mercury vapor lamp under oxygen deficiency it requires very marked reducing properties. This was shown in pigments of plants, iron, sulphur, dopa reaction, and the oxydation of adrenalin. This reducing property is lost if oxygen is added to the irradiated solution or if the irradiation takes place in the presence of oxygen. The reducing agent cannot be separated from the albumin by ultra-filtration but by heat coagulation. The germinal layer of irradiated pig skin reduced more than unexposed skin when testing it with the Unna stain. The authors conclude that the photochemical production of reducing sulfhydrate groups in irradiated skin is of importance for light biological effects. Although their experiments were carried out with solutions and on dead skin, similar processes probably take place in living skin during irradiation.

ERNST A. POHLE, M.D., Ph.D.

THE SKULL

Disease Pictures with Changes of the Inner Table of the Skull. Nicola Pende. München. med. Wchnschr., May 28, 1937, **84**, 855–858.

The author proposes the name "hyperostotic endocraniosis of Morgagni" for the "Stewart-Morel syndrome"—frontal hyperostosis with obesity of masculine distribution. He observes that association of cranial hyperostoses is often frontal, but occasionally elsewhere; sellar changes are characterized by thickening of the posterior clinoid processes or enlargement of the sella; increased digital markings; calcification of the falx; frequent intractable headache, with periodic continuous course; pathologic obesity of the hypogenital type; neuroses of the vegetative nervous system, and evidence of endocrine injury. The syndrome may resemble a number of other diseases when not typical. The changes in the base have been observed, in an increasing number of cases, accompanying the frontal hyperostoses; they suggest to the author either a chronic atrophic inflammation of the hypophysis or a tumor or hypertrophy, corresponding to which signs of hypophyseal insufficiency or over-function may be observed. The process is considered primary in the hypophyseal and tuber regions, exercising a secondary influence on the skull envelope. The Italian school considers it definitely inflammatory and infectious and possibly related to sinus disease.

Accepting the view of inflammatory origin, cure will depend on the difficulty of influencing a chronic hyperplastic osteitis, and of discovering the pathogenic factor in each case. Roentgen therapy with small doses or short wave diatherapy and very small doses to the frontal and hypophyseal regions, accompanied with injections of parathyroid extract, thyroxin, and posterior pituitary extract were tried. Results are not available.

The question of the identity of the author's cases, those hitherto described under the name "Stewart-Morel syndrome," and the first case of Morgagni, is discussed.

His illustrations show, in toxic cases of the disease, diffuse osteitis of other portions of the skull as well. Henschen describes changes which are similar, occurring in 40 per cent of women during the menopause. The author feels that further study of this question is needed.

LEWIS G. JACOBS, M.D.

THE SPINAL CORD

Rational Roentgen Therapy of Acute Non-suppurative Inflammation of the Spinal Cord. P. Del Buono. Strahlentherapie, 1937, **58,** 251.

Roentgen therapy offers the best results in the treatment of poliomyelitis in children. Less benefit may be expected in the same disease in adults, in multiple sclerosis, both the acute and chronic type. An analysis of the literature shows that the technic of irradiation, the quality and quantity of the rays used, has no fundamental effect on the end-result since successful treatment has been reported by various authors using entirely different technics. The author could not find any reports regarding radiation injuries of the spinal cord even following the application of large doses in young individuals.

ERNST A. POHLE, M.D., Ph.D.

THE STOMACH

Hernia of the Cardia of the Stomach. M. Jerzy Glass. Arch. d. mal. de l'app. digestif, 1937, **27,** 266–271.

The author describes the clinical and roentgenologic findings of a case of esophageal hiatus hernia in which he believes the condition is due to rachitic and emphysematous deformity of the thorax, causing distention of the esophageal hiatus and relaxation of the cardiac sphincters.

S. RICHARD BEATTY, M.D.

Gastric Lesions Simulating Cancer. R. Savignac. Arch. d. mal. de l'app. digestif, March, 1937, **27,** 233–247.

In a discussion of the differential diagnosis between gastric ulcer and carcinoma, the author presents three cases in which the roentgenologic studies indicated the presence of cancer, but in which the correct diagnoses were, respectively, alcoholic gastritis, old gastric ulcer with adhesions to the anterior abdominal wall, and a prepyloric ulcer. In each case, despite the roentgenologic findings, the clinical course did not confirm the impression of malignancy.

S. RICHARD BEATTY, M.D.

Experimental Observations in Gastric Ptosis. L. Gleize Rambal. Bull. et Mém. Soc. Radiol. Méd. de France, January, 1937, **25,** 66–70.

Consideration of the anatomy of the stomach and duodenum makes it evident that there is but one point of fixation or suspension for the stomach; this is at the cardia, where the stomach is supported by the esophagus, and by direct attachment of the fundus to the diaphragm.

The stomach rests on the mesocolon as on a shelf. When the colon is filled it rises in the abdomen due to the fact that the mesocolon and the small intestinal coils prevent motion in any other direction. This has been observed by roentgenologic study of the barium- or air-filled colon, with the patient upright.

Consequently, gastroptosis is, in the vast majority of cases, determined by coloptosis, and gastropexy is, for this reason, an illogical procedure.

S. RICHARD BEATTY, M.D.

Certain Radiologic Aspects of Cancer of the Stomach. A. Gutmann and Peristiany. Bull. et Mém. Soc. Radiol. Méd. de France, January, 1937, **25,** 5–9.

In addition to the usual radiologic appearance of cancerous lesions of the stomach, two forms are frequently seen which are always highly suspicious, if not diagnostic, of cancer: a large triangular niche without a break in the outline, often missed because it appears to form part of the normal profile of the stomach shadow, and another lesion, in the form of a deep pocket with stiff, straight sides and with a base that may or may not have a niche. These lesions are to be regarded as possibly cancerous and excised or followed closely by the radiologist during the course of therapy.

S. RICHARD BEATTY, M.D.

THE THYROID

Experimental Hyperthyroidism and its Treatment by Roentgen Rays. A. Jugenburg and B. Schlepakow. Strahlentherapie, 1937, **59,** 60.

The authors undertook an investigation to determine the mechanism of the therapeutic effect of roentgen rays in Basedow's disease. Dogs were given thyreokrin (by mouth) in order to produce the symptoms of hyperthyroidism. The animals that received treatment were irradiated according to the following technic: 180 kv., 0.5 mm. Zn + 3 mm. Al, 23 cm. F.S.D., 6 x 8 sq. cm. field, 360 r given three times at intervals of from six to seven days. A total of 10 dogs were used in the study. Careful observations were made of the behavior of the animals, their appetite, function of the gastro-intestinal tract, pulse, weight, iodine content of the blood, and basal metabolic rate. Further studies included the so-called Reid-Hunt reaction on mice and the effect of the blood of the dogs on the metamorphosis of larvæ of frogs. Under the influence of the drugs the dogs developed typical thyrotoxic symptoms in the course of three months. The first effect of radiation was seen in a drop of the basal metabolic rate, an increase in the body weight, and a return of the iodine content of the blood to normal values. After a period

of from four to five months the dogs were killed by means of chloroform and the thyroids studied histologically. A comparison of the control animals, the unirradiated and irradiated thyrotoxic dogs, showed that the glands of the control animals were the smallest; the irradiated animals had glands of about the same size as the untreated controls, and the unirradiated hyperthyrotoxic animals had the largest and heaviest thyroids. The histologic examination corresponded to the macroscopic appearance; the thyrotoxic unirradiated dogs had thyroids showing the typical picture of Basedow's struma.

After an analysis of their findings the authors conclude that the beneficial effect of roentgen rays in thyrotoxicosis cannot be due to a direct effect on the thyroid tissue but must be explained by an action on the vegetative nervous system.

ERNST A. POHLE, M.D., Ph.D.

TUBERCULOSIS, PULMONARY

Intrapleural Pneumolysis in Closing Tuberculous Cavitation. George L. Stivers. Jour. Am. Med. Assn., Jan. 16, 1937, **108,** 176–179.

The closure of a tuberculous cavitation by the elimination of pleuropulmonary adhesions necessitates a complete study of the intrathoracic cavity by intrapleural thoracopy. Thoracopy visualizes the contents of the pneumothorax cavity in the living subject and defines the anatomy of the lung and chest wall with a richness of true color that is distinctive.

The average results of compression in 100 cases of artificial pneumothorax in which some degree of collapse was obtained are considered. A complete collapse was established in approximately ten of these 100 cases. A selective collapse of the diseased area giving satisfactory results was attained in another ten cases. As a result of pleural adhesions that united the lung and chest wall, 80 cases remained in which lung collapse was ineffectual. Of these 80 cases, 20 were classified as a group in which, by continuous cautious pneumothorax therapy, a satisfactory partial collapse was brought about. Another 20 cases showed by roentgenologic examination that the pathologic process was so far advanced or so complicated that therapeutic pneumothorax was given only to prolong life.

Forty cases remained in which pleuropulmonary adhesions constituted mechanical obstructions that prohibited, even with the most careful pneumothorax technic, a satisfactory closure of cavitation. These patients were referred to the thoracic surgeon as possible subjects for intrapleural pneumolysis. About 15 of these cases were deducted for various prohibitive reasons. Among these were the presence of large fan-shaped, large round, or interlocking adhesions shown on the x-ray films, cavity prolongation into the adhesion, some purulent exudate, extensive contralateral pulmonary disease, very flexible mediastinum, or some other serious complication rendering them unsuitable for intrapleural pneumolysis. There were other cases found inpracticable at the time of operation after the thorascope had been introduced into the chest cavity (13 per cent of those accepted for operation), due to the presence of blood vessels, lung tissue, or caseous material in the adhesions.

Only 22 patients of the original 100 taking pneumothorax appeared to be appropriate subjects for intrapleural pneumolysis.

CHARLES G. SUTHERLAND, M.B. (Tor.).

TUMORS (DIAGNOSIS)

Pre-operative Diagnosis in Malignant Tumors. R. Huguenin. Le Cancer, 1935, **12,** 203–212.

The variety of modifications in neoplastic lesions and alterations in neighboring tissues produced by their presence make available methods of diagnosis, not excluding the histologic technics, uncertain. A single fragment of tissue, removed at biopsy, may include only benign or inflammatory tissue adjacent to the actual malignancy and lead to an erroneous diagnosis.

It is imperative that several fragments from different parts of a suspected region be examined. During thyroidectomy or mammectomy, for instance, repeated examinations from several fields furnish the only complete diagnosis of the lesion, its extent and variety. Following this plan one obtains information valuable, not only in guiding the extent of the operation, but in planning future therapy.

Transillumination of the breast preceding operation will allow one to mark down the zones from which fragments are to be removed for study as opacities of varying degrees are noted.

S. RICHARD BEATTY, M.D

The Pre-operative Visualization of Breast Tumors. N. Frederick Hicken, R. Russell Best, Charles F. Moon, and T. Tennyson Harris. Jour. Am. Med. Assn., March 13, 1937, **108,** 864–867.

Tumors of the breast can be visualized *in situ* by contrast roentgenographic studies. The neoplasms are rendered visible by outlining them with such contrast media as stabilized thorium dioxide sol, lipoiodine and air. This can be accomplished in one of two ways. The first method consists of injecting the milk ducts with the radiopaque substance and then making stereoscopic roentgenograms, which on study reveal an accurate anatomic pattern of the injected ductal system. Similar visualization studies can be made by inflating the breast tissues with air.

Mammograms not only locate the offending tumors but also determine the degree of involvement.

Aeromammograms (insufflations of air) are valuable in facilitating the diagnosis of breast tumors, particularly lipomas, fibro-adenomas, simple retention cysts, and carcinomas. They have, however, definite limitations; they do not visualize small papillomas, early carcinomas, small retention cysts, or cystic dilatation of the milk ducts.

The combination of ductal injection and the insufflation of air is ideal, for it permits a complete visualization of all the structures of the breast.

CHARLES G. SUTHERLAND, M.B. (Tor.).

TUMORS (THERAPY)

The Effect of Roentgen Therapy Applied to Normal Skin Areas on Tuberculous Lymphoma. H. Quastler. Strahlentherapie, 1937, **58,** 688.

The author has tried a method of treatment in patients with tuberculous glands consisting of the exposure of some normal skin areas on the abdomen or back in addition to local treatment over the involved glands. The "auxiliary radiation," as he calls it, consists of the exposure of 20 × 20 cm. sq. fields anteriorly and posteriorly twice on four successive days with 70 kv., 0.25 mm. Al, 40 cm. F.S.D., 10 r/min., 200 r per field and sitting. From two to four days later the involved glands are exposed with the same technic and given about 75–100 r effective in the diseased tissue. According to his experience, the response to this treatment is better than with local treatment alone, and although he cannot explain the mechanism of this effect, he believes that the procedure will improve our results.

ERNST A. POHLE, M.D., Ph.D.

Treatment of Malignancy. L. Schönbauer. Med. Klinik, Feb. 5, 1937, **33,** 185–188. (Reprinted by permission from British Med. Jour., April 10, 1937, p. 58 of Epitome of Current Medical Literature.)

The author evaluates modern methods of treatment of malignant tumors with surgery, x-rays, and radium by analyzing in the literature the percentage of successful results achieved in tumors of various parts of the body. He points out that radiological treatment is of value only in malignant tumors of which the parent tissue is radiosensitive. In this category belong the seminomas, folliculomas, lymphosarcomas, epitheliomas, and carcinomas. All others are radio-insensitive unless they are anaplasic—that is, completely differentiated from their parent tissue or through metaplasia converted into radiosensitive tumors. Surgical methods alone achieve success in the treatment of tumors of the brain (20 per cent), gastro-intestinal tract (30 per cent in radical removal), kidneys (25 per cent), bladder (30 per cent), and corpus uteri (60 per cent). X-ray and radium treatment is of more value than operation in tumors of the tonsils, thyroid, penis, testicle, and bones of the extremities. Tumors of the skin are successfully treated in 95 per cent of cases by any method. Cancer of the breast can be cured in 100 per cent of early cases by operation, but in its later stages irradiation in addition to surgery greatly improves the results. Combined surgical and radiological methods better the results by 15 per cent in tumors of the lips (72 per cent successes by operation alone); by 50 per cent in those of the tongue (15 per cent), and in those of the larynx and cervix uteri. Tumors of the esophagus, gall bladder, liver, pancreas, lung, and prostate are at present outside the category of successful results by any method, but the author is encouraged by the rapid strides made in radiological therapy to think that these and other inoperable tumors will eventually be successfully treated.

Roentgen Therapy of Mediastinal Tumors, with Report of Case of Lymphocytoma. M. Joly. Paris Méd., Feb. 6, 1937, **1,** 131–136. (Reprinted by permission from British Med. Jour., May 8, 1937, p. 75 of Epitome of Current Medical Literature.)

The author discusses the different types of mediastinal tumors and their treatment by x-rays. The most common mediastinal tumors are lymphosarcomas. They grow rapidly and soon invade the lungs, and they may also invade the pleura and pericardium. They may cause compression of the aorta, the large veins, or of the recurrent laryngeal, vagus, or phrenic nerves. These tumors are very radiosensitive. The author advises four fields for irradiation, namely, an anterior, two lateral, and a posterior field. He recommends the use of a deep therapy of 180 to 200 kilovolts, filtered through 0.5 mm. of copper with 1 mm. of aluminium, and large fields of about 15 by 15 cm. Wherever possible the first treatment should aim at the administration of 750 r to the tumor itself at the first sittings. This, however, may give rise to a severe reaction. In cases with considerable dyspnea it is therefore preferable to start the treatment with 625 r applied to the anterior field. If no severe reaction follows further doses of 625 r may be given daily to successive fields until each field has had a total of 3,500 r. In resistant cases the filtration may be increased to 1 mm. of copper and the total dose for each field to 4,500 r. Diuretics, laxatives, and daily warm baths are useful during the course of treatment.

A Case of Malignant Intracranial Tumor Reduced by Roentgen Therapy. A. Lambadaridis. Strahlentherapie, 1937, **59,** 175.

The author saw a patient with a tumor in the parietal bone which he diagnosed from the roentgenogram as "giant-cell or malignant sarcoma." He gave the patient two series of roentgen-ray treatments, one in June and July (16 sittings of 45 minutes each); the second series in October (20 sittings of 60 minutes each), and applied a total dose of 8,600 r at the rate of 4 r/min. The tumor responded promptly to the treatment and after three years the patient was still free from recurrence.

ERNST A. POHLE, M.D., Ph.D.

THE UTERUS

Serious Complications Encountered during Treatment of Carcinoma of the Uterine Cervix. Harry H. Bowing and Robert E. Fricke. Am. Jour. Roentgenol. and Rad. Ther., October, 1936, **36,** 490–497.

Of 541 patients referred for radiation therapy of carcinoma of the uterine cervix in the years 1930–1934, 91 per cent (495 patients) were accepted for treatment.

The number and severity of complications following radiation therapy of cervical cancer depend largely upon the extent of the malignancy and upon the patient's general health. Unfortunately the vast majority of the cases treated were in the inoperable (Stages III and IV) group. When the growth is too extensive for possible cure or when distinct metastases are demonstrated or when the patient's general health is impaired, limited treatment only is planned. In such cases only about one-third or one-fourth of the dosage used in complete treatment is administered. In spite of careful individual planning of the radiation dosage, 5.6 per cent of 495 cases treated, developed major complications, with death ensuing in 1.2 per cent of the cases. These complications are not to be considered the result of the treatment so much as the result of the acute inflammatory processes and infections which accompany malignancy. By dividing the radium doses, many of the common major complications such as pelvic cellulitis and hydronephrosis may be forestalled.

J. E. HABBE, M.D.

Clinical Results and Histologic Changes Following the Radiation Treatment of Cancer of the Corpus Uteri. A. N. Arneson. Am. Jour. Roentgenol. and Rad. Ther., October, 1936, **36**, 461–475.

Pre-operative roentgen treatment of corpus cancer appears to definitely enhance the results of surgery, whereas post-operative treatment only, appears less valuable. The combined use of radium and the x-ray, given before operation, probably accounts for the improved end-results. Hysterectomy alone produced better results in the author's cases than irradiation alone in the technically operable cases, although in patients which Grade III tumors, irradiation alone (radium plus x-rays) gave better results than operation only.

If operation is decided against, a course of external irradiation by divided dose technic should be administered first, to be followed by the insertion of radium. A full course of x-rays requires about 1,500 r to each of six fields, and 3,500–4,000 mg.-hr. of radium is the required dose of radium for a uterus of average length.

If hysterectomy is to be performed, pre-operative irradiation is advocated in every instance, but the technic is changed to single exposures to each pelvic field, following which radium is also used routinely.

Age, plus complicating additional conditions, may make a technically operable case seem better treated by irradiation only.

From histologic studies carried out following irradiation, the writer concludes that from five to ten threshold erythema doses must be delivered to every part of the tumor, to produce permanent sterilization of all tumor cells.

J. E. HABBE, M.D.

VON RECKLINGHAUSEN'S DISEASE

Study of von Recklinghausen's Disease. Y. Hiraga. Jap. Jour. Dermat. and Urol., Jan. 20, 1937, **41**, 1–6. (Reprinted by permission from British Med. Jour., May 15, 1937, p. 77 of Epitome of Current Medical Literature.)

The author describes his findings in 12 cases of von Recklinghausen's disease. Only one case showed the cardinal symptoms of skin and nerve tumors and large and small pigmented patches. One case occurred in a girl of 13. In two cases there were anomalies of hair and bone, and in eight the condition was found in other members of the family. In eight cases the skin was thickened and abnormally elastic in those parts affected by pigmentation and tumor formation. The most common changes in the cerebrospinal fluid were an abnormal globulin reaction, protein increase, and usually lymphocytosis. The fluid pressure was almost always raised. In four cases Hiraga obtained an encephalogram, one of which was normal, but in the remainder there was evidence of enlargement of the ventricles and the subarachnoid space. Nine cases in which the ear was examined all showed some abnormality. In six cases in which the vegetative nervous system was examined no etiological relation between it and the disease could be demonstrated. Hiraga found sudanophil cells, which are the phagocytes derived from the tumor cells, in eight cases. He irradiated the spine in two cases with the hope of affecting the skin tumors, but without any beneficial result. Hiraga believes von Recklinghausen's disease to be an hereditary anomaly in the same sense as a nevus.